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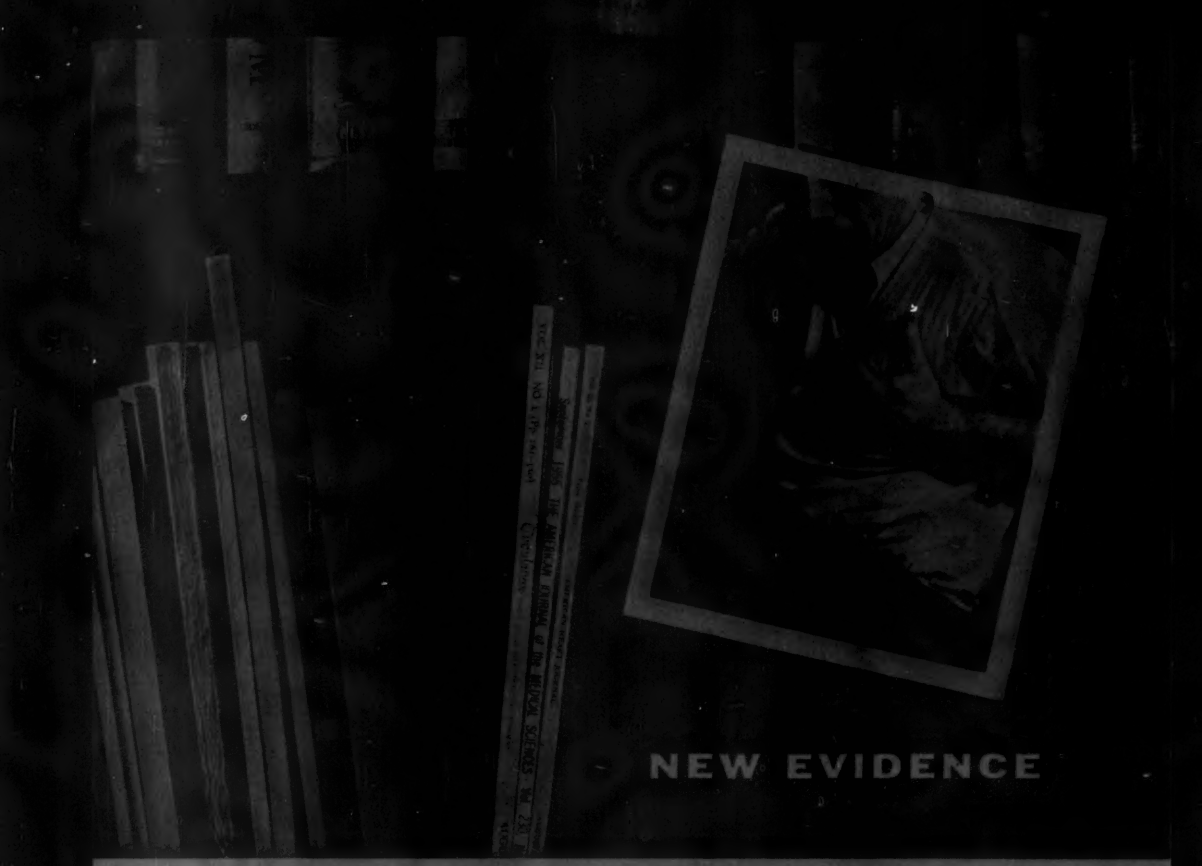

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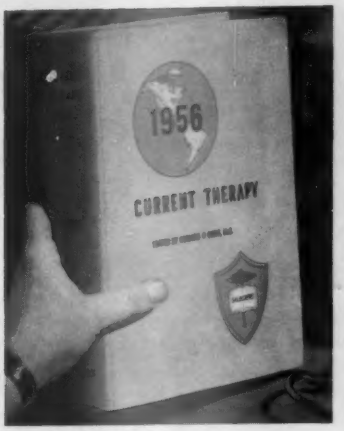

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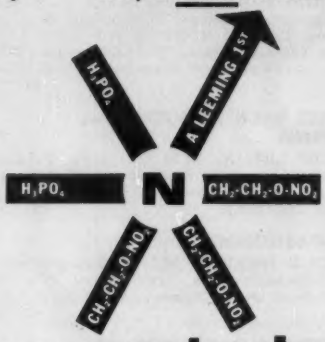

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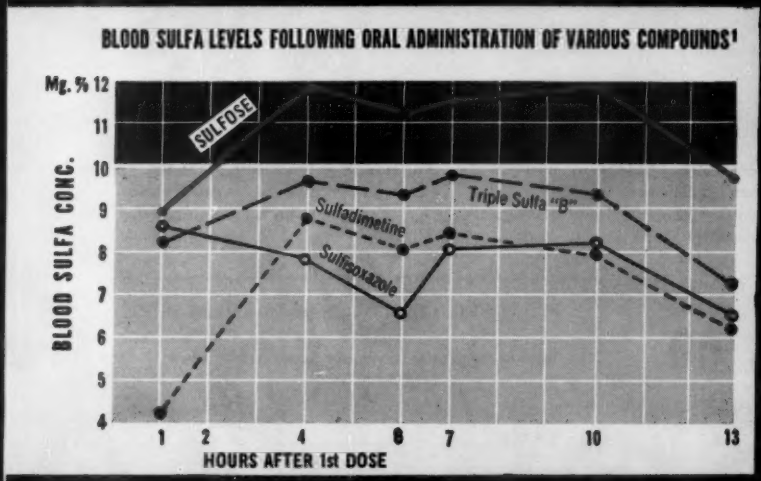
Suspension SULFOSE promotes the fullest response because it combines three potentiating sulfonamides in an alumina-gel base. Comparative studies show that this is the combination that induces ". . . both higher initial [and] more prolonged therapeutic levels."[1] Unlike single sulfonamides, Suspension SULFOSE couples threefold antibacterial action to multiple urinary solubility. For *effective* therapy with *maximal* renal safety.

Supplied: Suspension SULFOSE, bottles of 1 pint. Also available: Tablets SULFOSE, bottles of 100 and 1000.

1. Berkowitz, D.: Antibiot. & Chemo. 3:618 (June) 1953



Wyeth
Philadelphia 2, Pa.

sugar and spice and . . . gastric hyperacidity

Nice to taste . . . difficult to digest . . . the result, more often than not, will be gastric hyperacidity. Bad experiences and good intentions notwithstanding, this particular chain of misfortune is likely to recur. With Gelusil, however, excessive gastric acidity — whether acute or chronic — can be quickly and pleasantly relieved.

Sustained antacid action: The sustained action of magnesium trisilicate and specially prepared aluminum hydroxide gel restores and maintains a mildly acid gastric pH, without over-neutralizing or alkalizing. Gelusil thus avoids the twin dangers of acid rebound and systemic alkalosis.

Non-constipating: Gelusil's aluminum hydroxide component assures a low aluminum ion concentration; hence the formation of astringent — and constipating — aluminum chloride is minimal.

Dosage: 2 tablets or 2 teaspoonfuls two hours after eating or when symptoms are pronounced. Each tablet or teaspoonful provides: 7½ gr. magnesium trisilicate and 4 gr. aluminum hydroxide gel.

Gelusil®

ANTACID • ADSORBENT

WARNER-CHILCOTT

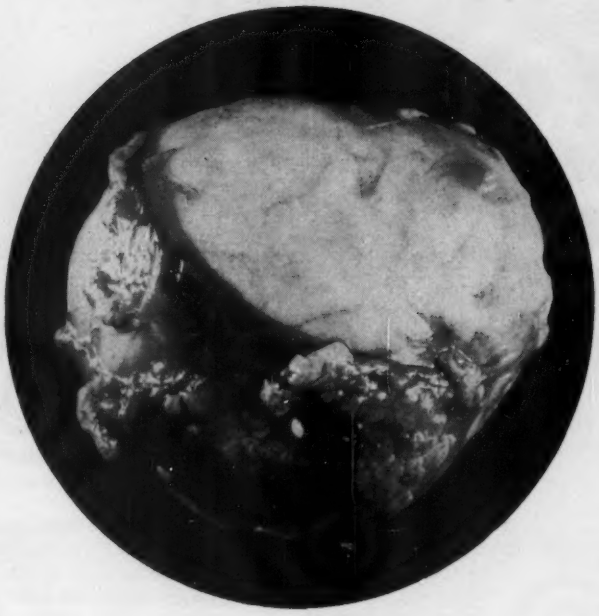
in nearly every
hypertensive patient
consider

PHEOCHROMOCYTOMA

and the

Regitine® test

Accurate, *specific* test for pheochromocytoma—simple and safe enough to be performed in the office unassisted. *New booklet* explains the REGITINE test step by step. Contact your CIBA representative or write Medical Service Division.



AMPULS, 5 mg. lyophilized Regitine methanesulfonate, each supplied with 1-ml. vial sterile distilled water; cartons of 1 and packages of 6 cartons.

TABLETS (oral), each containing 50 mg. Regitine hydrochloride; bottles of 100.

Regitine® methanesulfonate (phentolamine methanesulfonate CIBA)
Regitine® hydrochloride (phentolamine hydrochloride CIBA)

2/29870

CIBA *Summit, N.J.*

MEDICAL HORIZONS TV Monday P.M. *Sponsored by* CIBA ABC-TV

when it is essential that hypertension be reduced

Serpasil®-Apresoline®

hydrochloride

(reserpine and hydralazine hydrochloride CIBA)

Tranquilizer-Antihypertensive

The patient whose blood pressure *must* come down shows gratifying response to treatment with Serpasil-Apresoline, particularly after therapy with Serpasil alone. Among the benefits: both systolic and diastolic pressures reduced; heart rate slowed; renal blood flow enhanced; fewer side effects; decreased anxiety, stress and insomnia.

NOTE: Priming therapy with Serpasil adjusts the patient to the physiologic milieu of lower pressure.

Supplied: Tablets #2 (standard strength, scored), each containing 0.2 mg. Serpasil and 50 mg. Apresoline hydrochloride; Tablets #1 (half strength, scored), each containing 0.1 mg. Serpasil and 25 mg. Apresoline hydrochloride.

C I B A *Summit, N. J.*

2/22013M

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for your asthmatics...

effective, safe bronchodilation and sedation

rapid relief

unique base melts promptly after insertion . . . does not inactivate aminophylline . . . releases full therapeutic dose for quick bronchorelaxant and calming action

AMINET®

AMINOPHYLLINE WITH PENTOBARBITAL

Bischoff DIVISION

suppositories

exclusive nonreactive base

safer control

avoids gastric upsets of oral aminophylline . . . cardiovascular effects of adrenergics that preclude their prolonged use

Prescribe in boxes of 12: Full Strength *Aminet* Suppositories—aminophylline 0.5 Gm. (7½ gr.), sodium pentobarbital 0.1 Gm. (1½ gr.), benzocaine 0.06 Gm. (1 gr.). Also available, Half Strength *Aminet* and Plain Aminophylline Suppositories.

AMES COMPANY, INC. • ELKHART, INDIANA

AMES

03554

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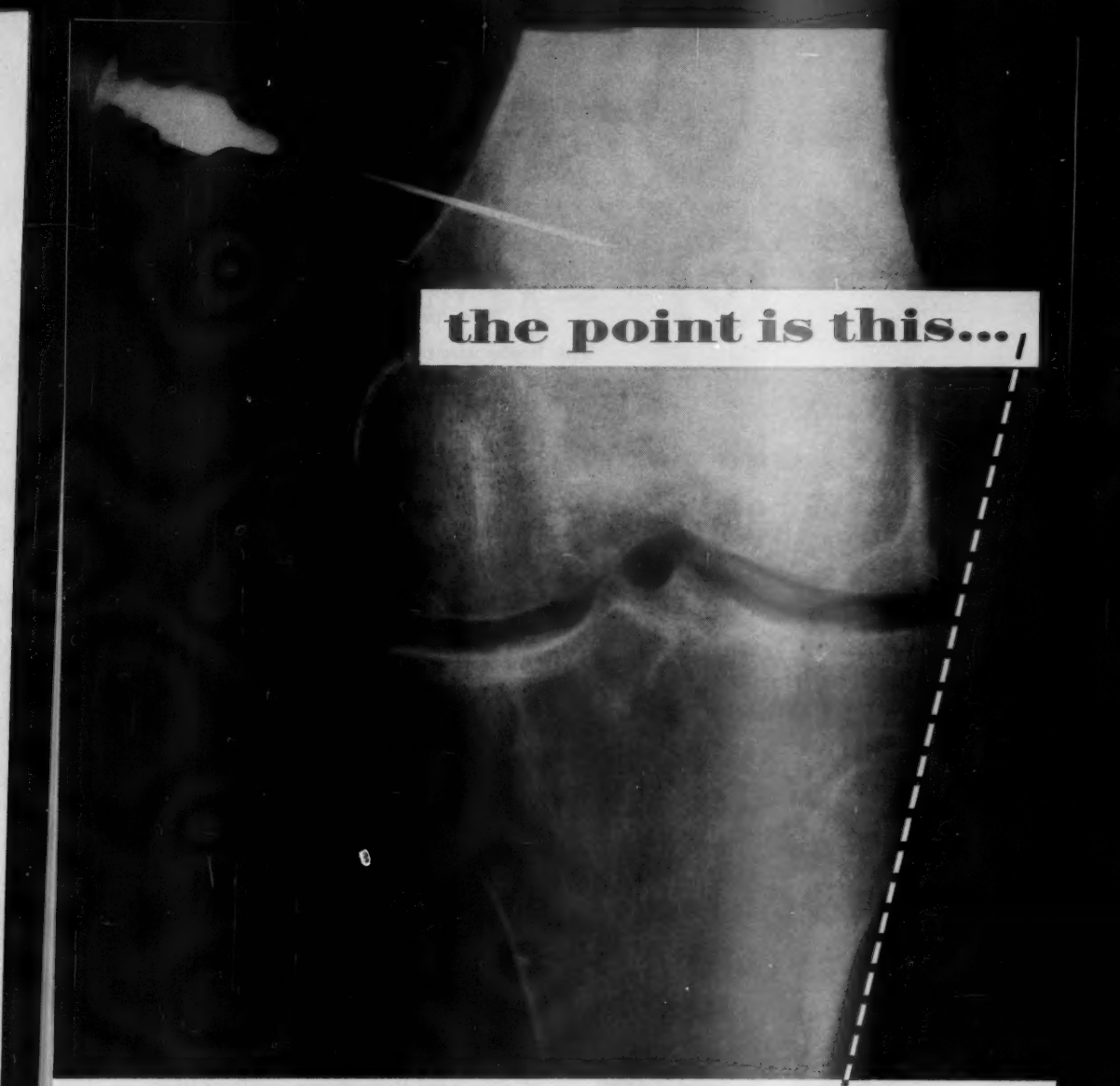

HydroCortone® -T B A

(HYDROCORTISONE TERTIARY-BUTYLACETATE, MERCK)

gives the arthritic patient more days of freedom from joint symptoms—in many patients the anti-rheumatic effect persists 2 to 10 times longer than after injection of hydrocortisone acetate. Its action is local and without systemic effect.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

SUPPLIED: SALINE SUSPENSION HYDROCORTONE-TBA—25 MG./CC., VIALS OF 5 CC.

DID you ever stop to think that the many men and women who have a hand in the fabrication, assembly, testing, etc., of equipment you purchase are, in a very major way, responsible for its performance in your practice?

That is why wise manufacturers today consider strongly the *personal equation* along with such requirements as high quality purchasing and production control.

WHO PROFITS

when you buy a Viso-Cardiette?

There's a good reason why, at Sanborn Company, the employees who make the Viso-Cardiette are *concerned* with the manner in which the instruments provide, or do not provide, the service for which the purchase is made. For, when the company makes a profit *they receive a substantial share of it!* This has been going on *since 1917.* Also, the great majority of these same men and women *own* Sanborn Company, being stockholders as well.

It follows that an employee who has a definite stake in the instruments his company makes, and the dollars received from their sale, takes a lively and whole-hearted interest in doing *his* job *better.* You can see this in the daily attitude of Sanborn employees. And, they aren't the only ones who profit from better instruments. You do, too, Doctor.

Descriptive literature on the Viso-Cardiette, and details of a 15-day no obligation clinical test plan will be sent on request. If you wish a copy of our Annual Report, we will gladly send you that also.

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Romilar—
a real
cough specific

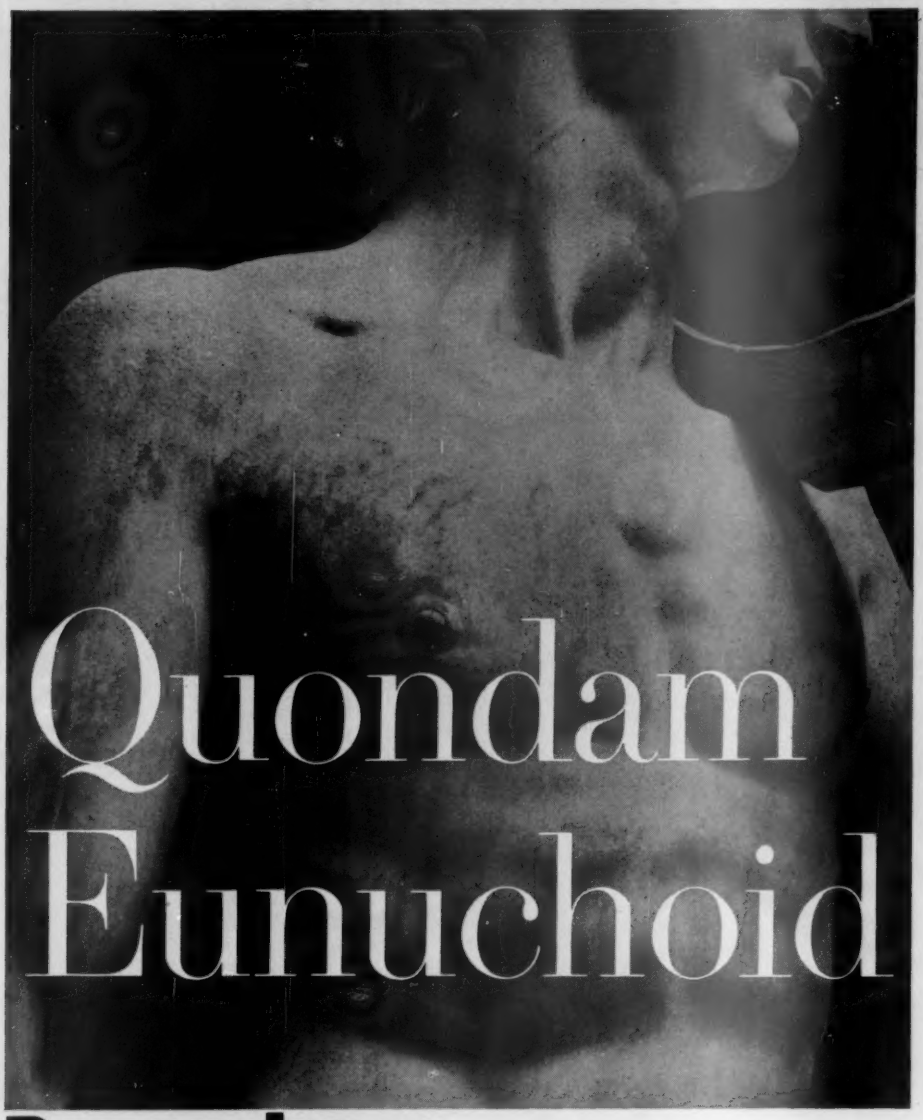
A 10-mg dose of Romilar
equals a 15-mg dose
of codeine in specific
antitussive effect.
Yet Romilar® 'Roche' is
non-narcotic; it does
not cause drowsiness,
nausea or constipation.
Tablets, 10 mg; syrup,
10 mg/4 cc; expectorant,
15 mg Romilar plus
90 mg ammonium chloride
per 5 cc.

ROCHE
Original Research
in Medicine and Chemistry

Deputy Doctor—

Once she gets home from the hospital, Mother becomes your deputy in seeing that the newborn youngster gets his daily vitamin needs. And she'll find it easy if you prescribe Vi-Penta® Drops. Just 0.6 cc added to the formula daily provides the required A, C, D, and B vitamins (including B_6), and you know they're stable and potent because they're dated.

Hoffmann-La Roche Inc • Nutley • N.J.



Perandren® phenylacetate
(testosterone phenylacetate CIBA)

Clinically pre-eminent for potency and duration of androgenic/anabolic activity.

Usual schedule: One injection a month.

Usual response: Smooth improvement, due to potent, well-sustained androgenic and/or anabolic action.

Multiple-dose Vials, 10 ml., each ml. containing 50 mg. Perandren phenylacetate (with 1% procaine hydrochloride).

8/3224M

CIBA
SUMMIT, N.J.

For assured dependability in Digitalis administration

Physiologically Standardized

Pil. Digitalis (Davies, Rose)

0.1 Gram (approx. 1½ grains)

Comprise the entire properties of the leaf.

Clinical samples sent to physicians on request.

Davies, Rose & Company, Limited — Boston 18, Massachusetts

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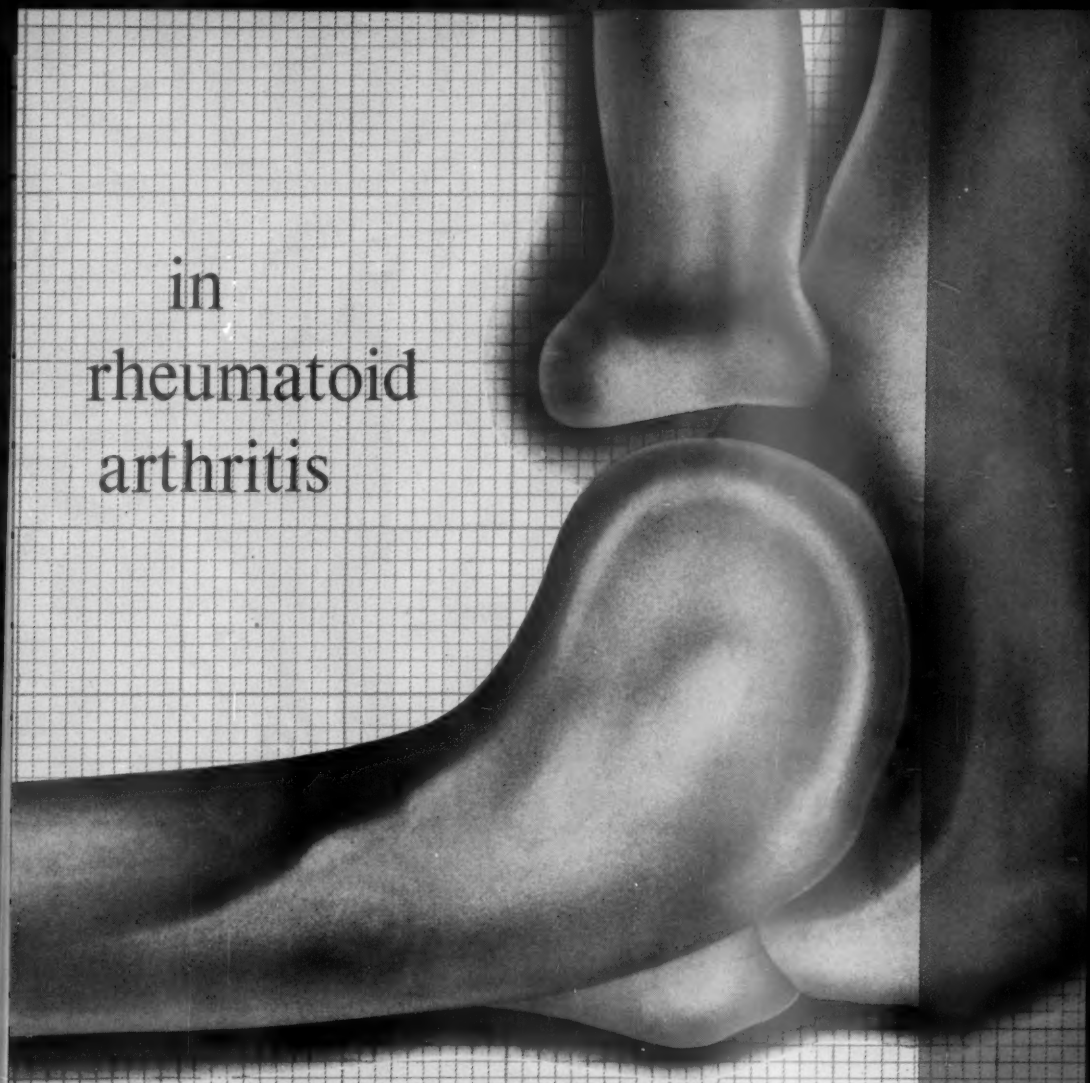

in rheumatoid arthritis

replaces cortisone and hydrocortisone
permits treatment of more patients

METICORTEN*

(PREDNISONE, SCHERING)

Schering

- significantly less edema due to sodium retention
- excellent relief of pain, swelling, tenderness
- effective in smaller dosage

*T.M.

MC-J-63-1255

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ACHROMYCIN*

Tetracycline
Lederle

widely prescribed because of these important advantages:

1) rapid diffusion and penetration
2) prompt control of infection
3) true broad-spectrum activity (proved effective against a wide variety of infections caused by Gram-positive and Gram-negative bacteria, rickettsiae, and certain viruses and protozoa)
4) negligible side effects
5) every gram produced in Lederle's *own* laboratories under rigid quality control, and offered *only* under the Lederle label
6) a *complete* line of dosage forms

in prolonged illness, prescribe

ACHROMYCIN SF

TETRACYCLINE with STRESS FORMULA VITAMINS

Attacks the infection, bolsters the body's natural defense. Stress vitamin formula suggested by the National Research Council in *dry-filled, sealed* capsules with ACHROMYCIN, 250 mg. Also available: ACHROMYCIN SF ORAL SUSPENSION (Cherry Flavor), 125 mg. per 5 cc.

dry filled sealed capsules
(a Lederle exclusive!) for more rapid and complete absorption. No oils, no paste, tamperproof!

LEDERLE LABORATORIES DIVISION *AMERICAN Cyanamid COMPANY* PEARL RIVER, NEW YORK Lederle

®REG. U.S. PAT. OFF.

THIS IS

Rauwiloid®

a preparation of choice in the treatment of HYPERTENSION

- Rauwiloid represents the balanced, mutually potentiated actions[1] of several Rauwolfia alkaloids, of which reserpine and the equally antihypertensive rescinnamine have been isolated.
- Hence, reserpine is not the total active antihypertensive principle of the rauwolfia plant.
- Rauwiloid, the alseroxylon fraction of Rauwolfia serpentina, Benth., is freed of the undesirable alkaloids of the whole root. Recent investigations confirm the desirability of Rauwiloid (because of the balanced action of its contained alkaloids) over single alkaloidal preparations; "...mental depression...was...less frequent with alseroxylon..."[2]

The dose-response curve of Rauwiloid is flat, and its dosage is uncomplicated and easy to prescribe . . . merely two 2mg. tablets at bedtime.

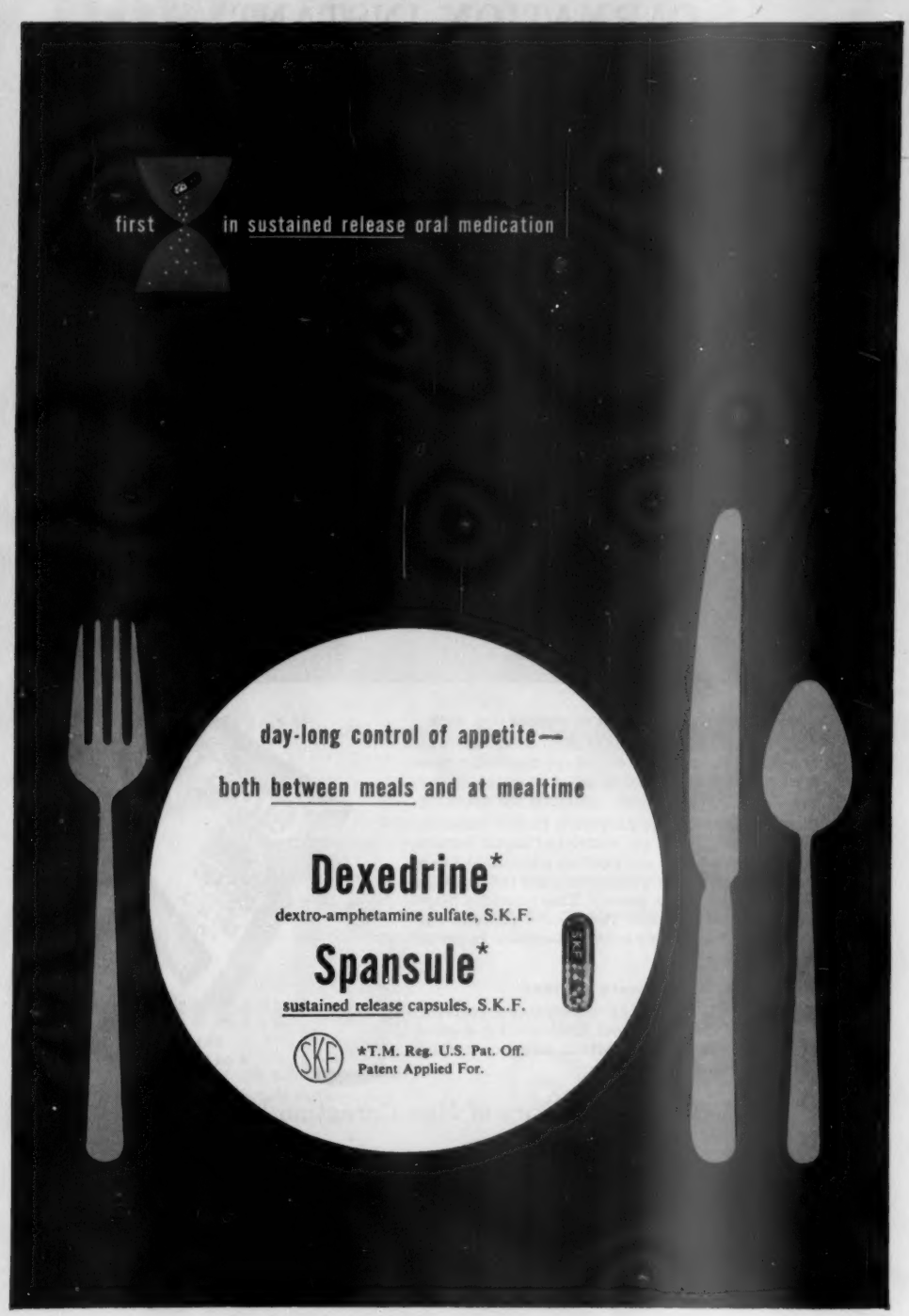
1. Cronheim, G., and Toekes, I.M.: Comparison of Sedative Properties of Single Alkaloids of Rauwolfia and Their Mixtures. Meeting of the American Society for Pharmacology and Experimental Therapeutics, Iowa City, Iowa, Sept. 5, 1955.

2. Moyer, J.H.; Dennis, E., and Ford, R.: Drug Therapy (Rauwolfia) of Hypertension. II. A Comparative Study of Different Extracts of Rauwolfia When Each Is Used Alone (Orally) for Therapy of Ambulatory Patients with Hypertension. A.M.A. Arch. Int. Med. *96*:530 (Oct.) 1955.

Riker

LOS ANGELES

Rauwiloid is the original alseroxylon fraction of India-grown Rauwolfia serpentina, Benth., a Riker research development.



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CARNATION INSTANT
overcomes "diet resistance" because it tastes so good!

New CRYSTAL FORM of nonfat dry milk

Only the Carnation crystal form mixes instantly even in ice-cold water...stays fresh and free-flowing on the pantry shelf. And *most* important, the flavor is *fresh*, delicious for drinking.

For the patient who prefers a richer flavor in nonfat milk, or is on restricted liquid intake, the physician may suggest an additional heaping tablespoon of crystals per glass (or an extra ⅓ cup crystals per quart). This provides heavier, richer flavor—and *25% more protein, calcium and B-vitamins with no increase in fat or liquid bulk.*

AVAILABLE IN 3 OR 8-QT. PACKAGE

Top Food Award Winner

The Carnation crystals process received the biennial Food Engineering Award as the most important advance in food processing.

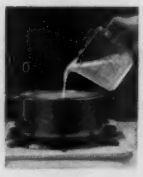
Other Superiorities of New Carnation Instant

MIXES INSTANTLY

Carnation Instant crystals mix instantly with a light stir, even in ice-cold water—ready to drink.

STORES ON SHELF

Carnation crystals do not harden in package. Costs up to 7¢ less per quart than bottled nonfat milk.



NO SPECIAL RECIPES

Liquid Carnation (regular or "self-enriched") is simply used in any recipe calling for milk.

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NOW

Ferrous Iron with Vitamin C

for simple
specific
rapid
economical

correction of iron deficiency anemias

"Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid . . ."*

"CYTOFERIN"—*the logical combination for iron therapy.*

- Iron in the readily absorbed ferrous form.
- Vitamin C to maintain acidity in the upper intestinal tract for greater iron absorption.
- Vitamin C as a reducing agent for the ferric iron obtained from food.
- Vitamin C for hypochromic microcytic anemias, which will not respond to oral iron therapy alone.

"CYTOFERIN"—*the direct approach to greater iron absorption.*

Each tablet contains:
Ferrous sulfate exsic. (3 gr.) . . . . . 200 mg.
Vitamin C (ascorbic acid) . . . . . 150 mg.

Dosage: 1 tablet two or three times daily, taken preferably with meals.

Supplied: No. 705, bottles of 100 and 1,000.

NEW PRODUCT

*Sacks, M. S.: Ann. Int. Med. *42*:458 (Feb.) 1955.

Ayerst

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

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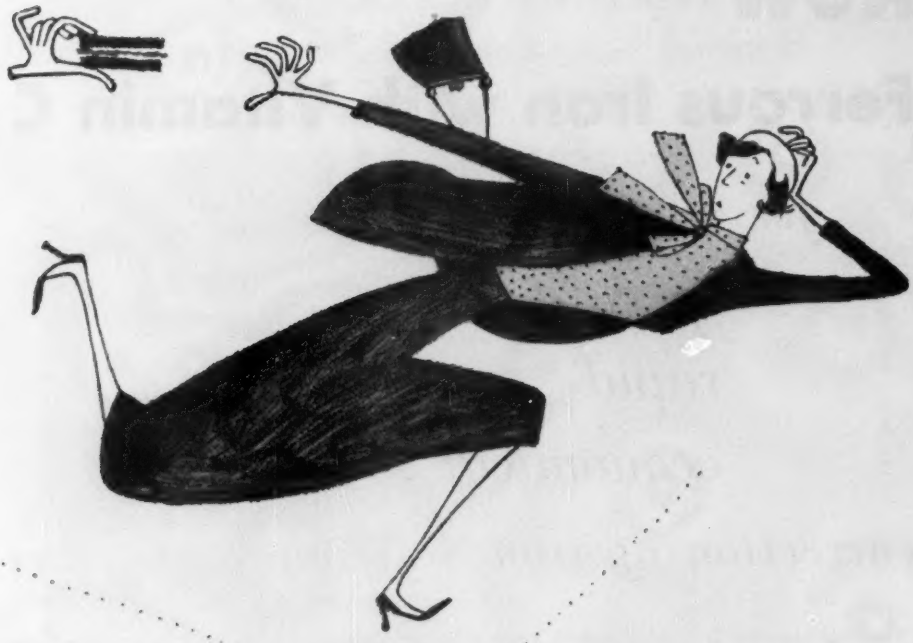

quick—

what's a good

B complex?

sur-Bex® with C

(ABBOTT'S B-COMPLEX TABLETS WITH C)

Each SUR-BEX with C tablet supplies:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} (as vitamin B_{12} concentrate)	2 mcg.
Pantothenic Acid (as calcium pantothenate)	10 mg.
Ascorbic Acid	150 mg.
Liver Fraction 2, N.F	300 mg. (5 grs.)
Brewer's Yeast, Dried	150 mg. (2½ grs.)

Abbott

As a dietary supplement: 1 or 2 tablets daily.

For stress, or postoperative convalescence: 2 or more tablets daily.

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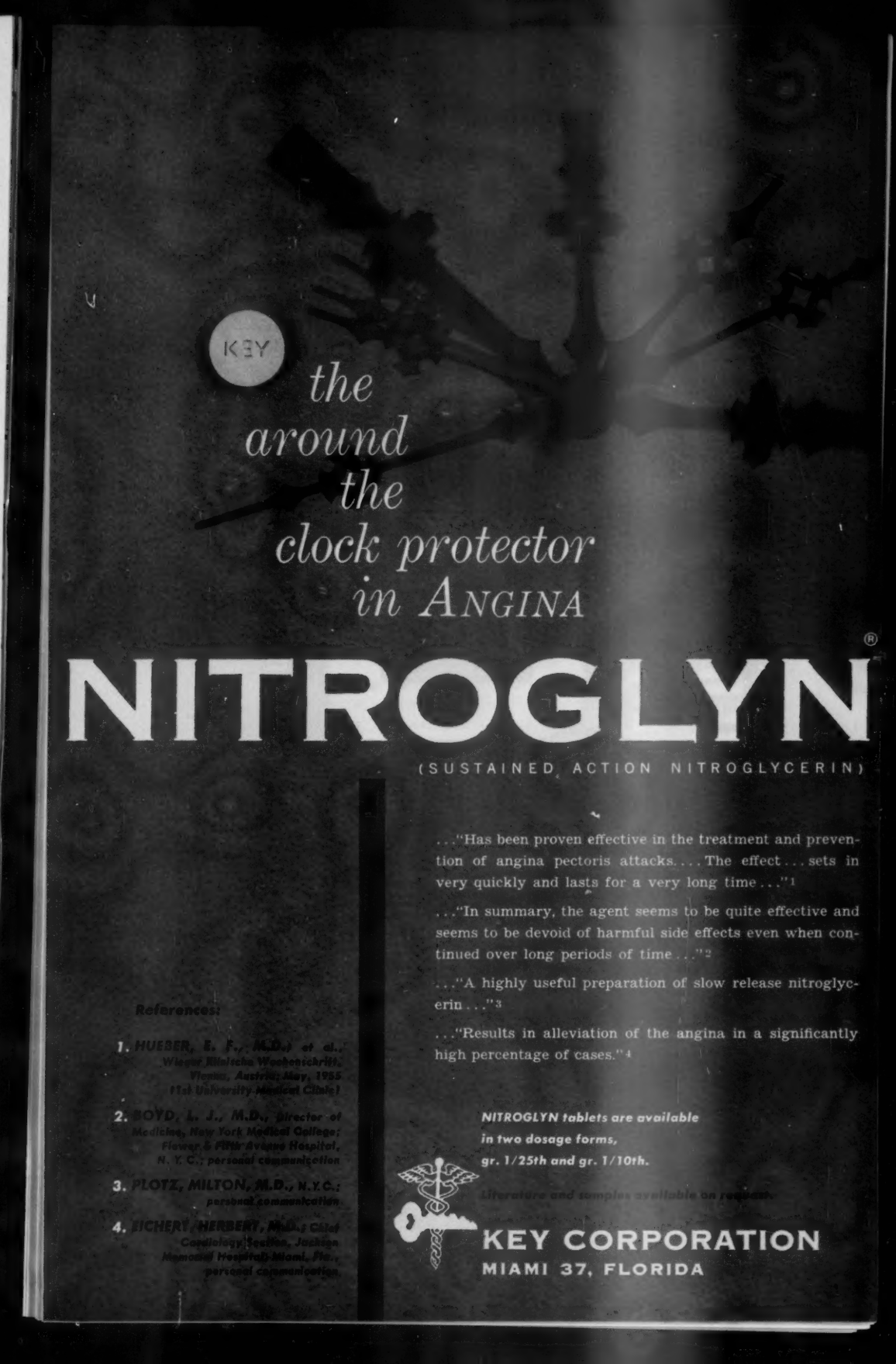

the around the clock protector in ANGINA

NITROGLYN®

(SUSTAINED ACTION NITROGLYCERIN)

..."Has been proven effective in the treatment and prevention of angina pectoris attacks.... The effect... sets in very quickly and lasts for a very long time..."[1]

..."In summary, the agent seems to be quite effective and seems to be devoid of harmful side effects even when continued over long periods of time..."[2]

..."A highly useful preparation of slow release nitroglycerin..."[3]

..."Results in alleviation of the angina in a significantly high percentage of cases."[4]

NITROGLYN tablets are available in two dosage forms, gr. 1/25th and gr. 1/10th.

Literature and samples available on request.

KEY CORPORATION
MIAMI 37, FLORIDA

References:

1. **HUEBER, E. F., M.D., et al.,** *Wiener Klinische Wochenschrift, Vienna, Austria; May, 1955 (1st University Medical Clinic)*
2. **BOYD, L. J., M.D.,** *Director of Medicine, New York Medical College; Flower & Fifth Avenue Hospital, N. Y. C.; personal communication*
3. **PLOTZ, MILTON, M.D., N.Y.C.:** *personal communication*
4. **EICHERT, HERBERT, M.D.,** *Chief Cardiology Section, Jackson Memorial Hospital, Miami, Fla., personal communication*

LEVOPHED®
in coronary
shock
saves 20 per cent more lives[1]

Among 131 patients in **severe** shock due to myocardial infarction, Levophed saved the lives of 53[1] — a remarkable salvage rate where ordinarily there is an 80 to 90 per cent mortality rate.[2]

Intravenously administered Levophed is almost **twice** as effective in relieving shock and saving lives as expectant treatment — transfusions and older pressor agents.[1] "Survival occurred in two-fifths of patients treated with levarterenol [Levophed] and in only one-fifth of patients treated expectantly."[1]

Because delay may be disastrous[3] Levophed should be used **first** and promptly.

Levophed raises blood pressure within 10 to 30 seconds — maintains it almost indefinitely. Unlike other agents, Levophed produces an increase in coronary blood flow and oxygen supply to the myocardium far in excess of the rise in mean blood pressure.[4] Levophed limits the size of the infarct and saves healthy myocardium.[5]

LEVOPHED
(levarterenol bitartrate)
natural antishock pressor hormone

1. Dillon, M. J., et al.: **Am. Jour. Med.**, 18:622, Apr., 1955. 2. Sampson, J. J.; and Zipser, Albert: **Circulation**, 9:38, Jan., 1954. 3. Nichol, E. S., in Conn, H. F.: Current Therapy 1954. Philadelphia, W. B. Saunders Co., 1954, p. 196. 4. Jamison, W. L., et al.: **Jour. Am. Geriat. Soc.**, 3:521, Aug., 1955. 5. Gilchrist, A. Rae: **Brit. Med. Jour.**, 2:351, Aug. 16, 1952.

Levophed (brand of levarterenol), trademark reg. U. S. Pat. Off.

Winthrop LABORATORIES • New York 18, N.Y. • Windsor, Ont.
(Formerly Winthrop-Stearns Inc.)

a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried	0.12 Gm.
Calcium ascorbate (equivalent to 50 mg. ascorbic acid)	60 mg.
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

BRISTOL, TENNESSEE
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The S. E. Massengill company

IT'S A CAMBRIDGE

The Cambridge "Simpli-Scribe"

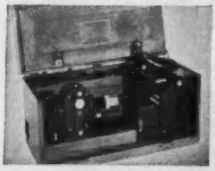
Model Electrocardiograph has important design features not found in any other Direct Writing Electrocardiograph. Its platen is concave to compensate for the arc described by the writing stylus. As a result, its records are true rectilinearly without tangential error and accordingly do not require correction for accurate interpretation.

The entire writing mechanism of the Simpli-Scribe is rugged, and yet it is extremely light in weight. This means a minimum of inertia and friction, low power requirement and resultant higher accuracy. The entire instrument is designed for light weight and convenience. For example, replacement of the paper roll is just a matter of snapping it into position. Simple means are provided for checking not only the standardization of stylus deflection, but also for checking accuracy of timing of the records as well. The controls are minimum in number and conveniently grouped for ease of operation.

The Simpli-Scribe is a fine instrument worthy of its Cambridge nameplate. It provides the Cardiologist, Clinic or Hospital with a direct writing Electrocardiograph of utmost usefulness and accuracy.

"SIMPLI-TROL" PORTABLE MODEL ELECTROCARDIOGRAPH

A string galvanometer instrument . . . the standard of comparison, light in weight and simple to operate. Entire equipment in one mahogany case, 8" x 19" x 10"; weight 30 pounds. May be arranged for heart sound and pulse recording.



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CAMBRIDGE ALSO MAKES: the Standard String Galvanometer and Direct Writer Electrocardiographs in Multi-Channel Models, Catheterization Monitor-Recorders, Operating Room Cardioscopes, Educational Cardioscopes, Electrokymographs, Plethysmographs, Amplifying Stethoscopes, Research pH Meters, Automatic Continuous Blood Pressure Recorders and Instruments for Measuring Radioactivity.

CAMBRIDGE
ELECTROCARDIOGRAPHS

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for balance in cardiac control

DIGOXIN 'B.W. & CO.'®

a conveniently administered dosage form for every need

for simplified emergency digitalization:

'WELLCOME' ® brand **DIGOXIN INJECTION**
0.5 mg. in 2 cc.

may be given intramuscularly, as well as intravenously, without dilution
Boxes of 12 and 100 ampuls

for dependable maintenance:

'TABLOID' ® brand **DIGOXIN** ***0.25 mg.*** *Scored (white)*
Bottles of 100 and 1,000 tablets

'TABLOID' ® brand **DIGOXIN** ***0.5 mg.*** *Scored (green)*
Bottles of 100 and 1,000 tablets

for infants and children:

'WELLCOME' ® brand **DIGOXIN ELIXIR PEDIATRIC**
0.05 mg. in each cc.

Supplied with a dropper calibrated to 1 cc. in graduations of 0.2 cc. (0.01 mg. Digoxin)
Bottles of 2 fluid ounces

BURROUGHS WELLCOME & CO. (U.S.A.) INC., *Tuckahoe, New York*

new... paired piperidol action
for functional gastrointestinal complaints

rapid
visceral eutonic, Dactil*

prolonged
cholinolytic, Piptal†

relief throughout the G. I. tract

Tridal

TRIDAL permits more comprehensive control of gastrointestinal complaints by providing the combined benefits of two piperidols. The local action of Dactil* works immediately to give **rapid** relief of gastrointestinal pain and spasm; the potent cholinolytic Piptal† reinforces relief and provides **prolonged** normalization of secretion and motility.

TRIDAL is singularly free from urinary retention, constipation, dry mouth, blurred vision.

dosage: One TRIDAL Tablet two or three times a day and at bedtime. Unless rapidly swallowed with water, TRIDAL will produce some lingual anesthesia.

Each TRIDAL Tablet contains 50 mg. of Dactil and 5 mg. of Piptal. Bottles of 50 compressed, uncoated tablets.

*Dactil (the *only* brand of N-ethyl-3-piperidyl diphenylacetate hydrochloride): the piperidol to prescribe alone when no interference with digestive secretion is desired.

†Piptal (the *only* brand of N-ethyl-3-piperidyl-benzilate methobromide): the piperidol to prescribe alone when peptic ulcer is known to be present and normalization of secretion as well as motility is desired.

Lakeside Laboratories, Inc. PIONEERS IN PIPERIDOLS MILWAUKEE 1, WISCONSIN

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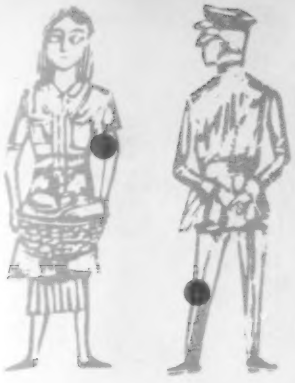
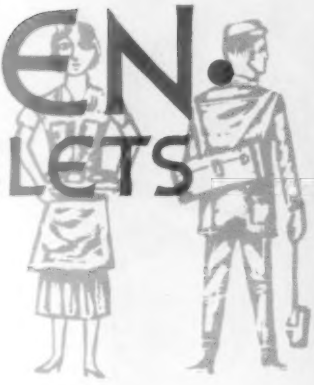


SIGMAGEN TABLETS



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acetylsalicylic acid (325 mg.)
vitamin C (20 mg.)
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METICORTEN (0.75 mg.)

for relief in

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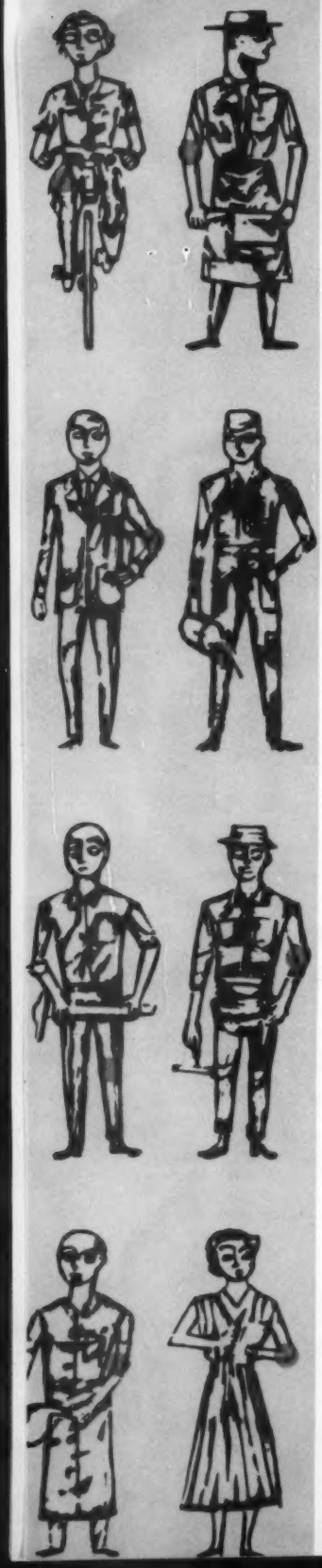

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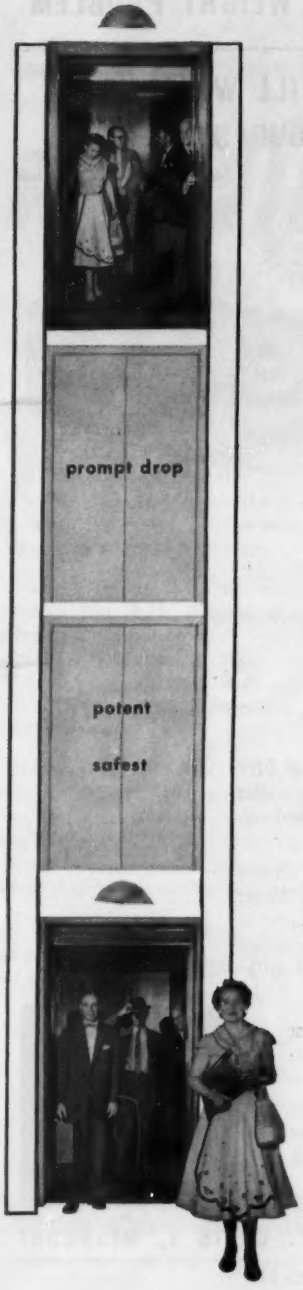

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Rauvera represents the *safest* hypotensive *combination therapy* because the additive if not *synergistic* action of purified combined Rauwolfia alkaloids (alseroxylon) with a lower dosage of the alkavervir fraction of Veratrum viride (biologically standardized for hypotensive action) produces considerably less side effects than when alkavervir is used alone. Rauvera never causes postural dizziness because it does not contain ganglionic blocking agents.

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the safest combination for hypotensive therapy

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THEOBROMINE SODIUM ACETATE

plus **RAUWOLFIA** *serpentina*

FOR ESSENTIAL HYPERTENSION

FOR YEARS *Thesodate*, the original enteric-coated tablet of Theobromine Sodium Acetate, has been used extensively for cardiac and circulatory disorders such as coronary artery disease which is often accompanied by hypertension.

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in following formulas

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7½ gr. with ½ gr.
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WITH POTASSIUM IODIDE
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WITH POTASSIUM IODIDE AND PHENOBARBITAL
5 gr. with 2 gr. and ¼ gr.

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ENTERIC-COATED

Supplied in
100's and 500's

Each enteric-coated tablet contains:

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Rauwolfia serpentina ..... 50 mg.

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And still her night keeps
ticking away: no sleep . . . no
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is enough to erase anxiety,
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short duration of effect, wide
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in equal doses, no other
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briefer, more profound effect.

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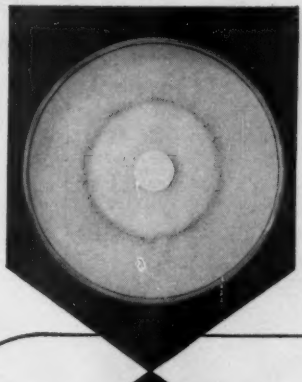

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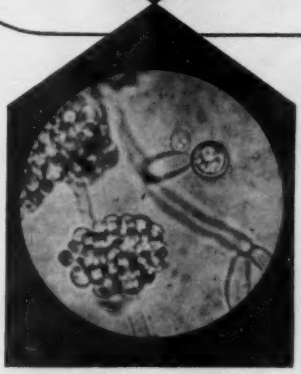

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Because it contains Mycostatin (Squibb Nystatin), the first safe antifungal antibiotic, MYSTECLIN acts to prevent monilial overgrowth frequently observed during broad spectrum antibiotic therapy. Manifestations of this overgrowth may include some of the diarrhea and anal pruritus associated with antibiotic therapy, as well as vaginal moniliasis and thrush. On occasion, serious and even fatal infections caused by monilia may occur.

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(Squibb Tetracycline-Nystatin)

Each MYSTECLIN Capsule contains 250 mg. Steclin (Squibb Tetracycline) Hydrochloride and 250,000 units Mycostatin (Squibb Nystatin).

Minimum adult dose: 1 capsule q.i.d. *Supply:* Bottles of 12 and 100.

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for comprehensive antidiarrheal therapy . . . for the whole family

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References: 1. Poth, E. J., J.A.M.A. 153:1516 (Dec. 26) 1953.

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References: (1) Bruses, D. D.: J. Nerv. & Ment. Dis. *121*:67, 1955. (2) Koppanyi, T.; Morgan, C. F., and Princiotto, J. V.: J. Am. Pharm. A. (Scient. Ed.) *44*:221, 1955. (3) Fasekas, J. F., and Koppanyi, T.: To be published. (4) Steininger, E.: Prakt. Arst *7*:224, 1953.

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References: 1. Ehrlich, J. C.: Arizona Med. *12:* 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. *227:* 188 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. *39:* 1189 (Dec.) 1953. 4. Hejtmancik, M. R., and Herrmann, G. R.: Texas St. J. M. *51:* 238 (May) 1955. 5. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation *5:* 201 (Feb.) 1952. 6. Denham, R. M.: J. Kentucky St. M. Assoc. *53:* 209 (Mar.) 1955.

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Digitalis leaf	0.1 Gm.	0.5 mg.
Digitoxin	0.1 mg.	0.5 mg.
Digoxin	0.5 mg.	0.5 mg.

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Supplied: *Suspension*, bottles of 12 fluidounces. *Tablets*, bottles of 100. Samples sent promptly on request.

1. Kramer, P.: Med. Clin. North America, 39:1381, Sept. 1955.
2. Morrison, Samuel: Am. J. Gastroenterology 22:309 (1954).
3. Rossett, N. E., Rice, M. L., Jr., Gastroenterology 26:490 (1954).

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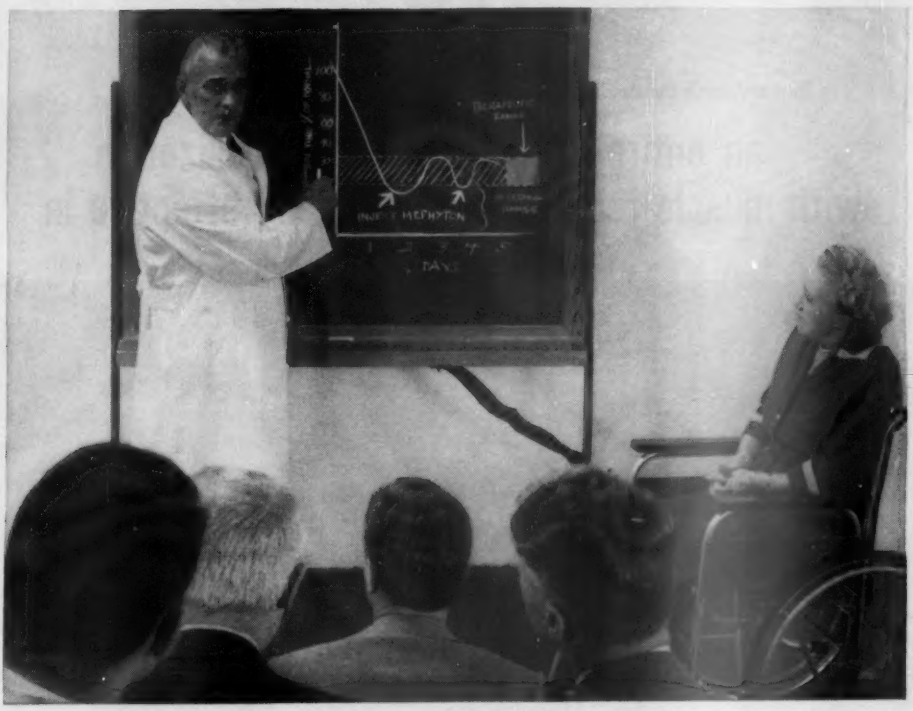

MAJOR ADVANTAGES: Action detectable within 15 minutes, prothrombin time normalized within 4 to 12 hours, bleeding checked in 3 to 6 hours.

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1. Gamble, J. R., *et al.*, *Arch. Int. Med.* 95:52, January 1955.

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1. Selling, L. S.: J.A.M.A. 157: 1594, 1955. 2. Borrus, J. C.: J.A.M.A. 157: 1596, 1955.

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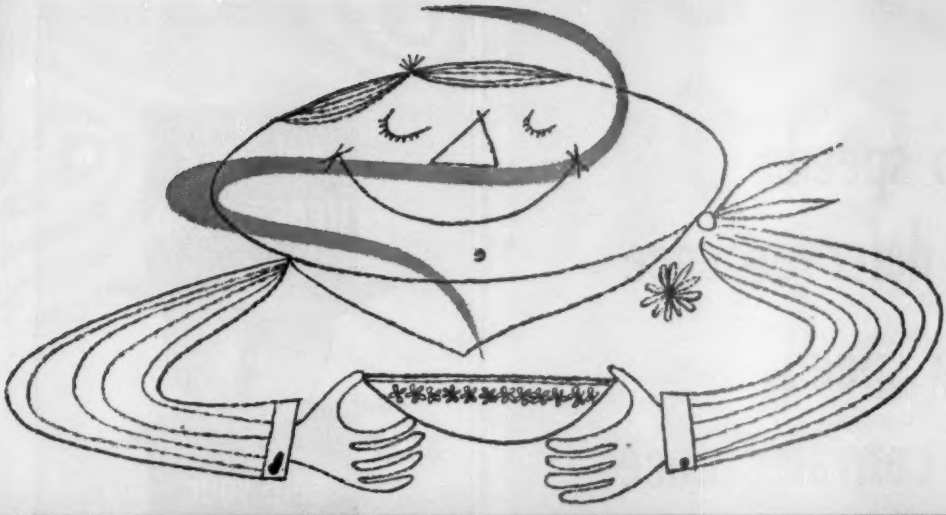

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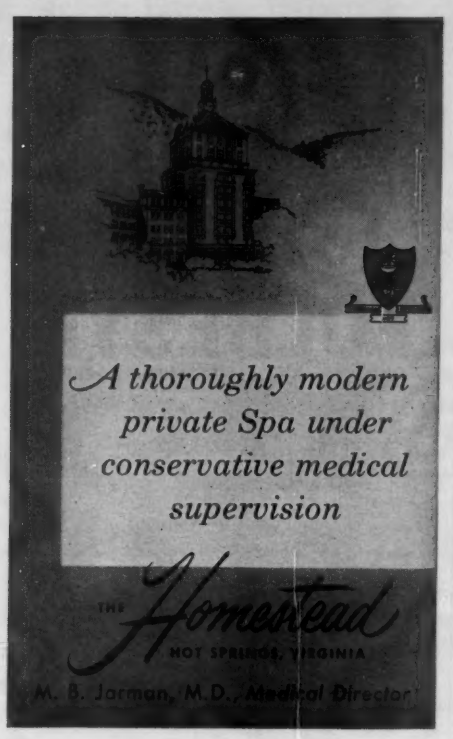

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Vol. 42, No. 2, February, 1955
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1. Johnston, R.L.: J. Indiana St. M.A. 46:869, 1953. 2. McHardy, G., and Browne, D.: Southern M. J. 45:1139, 1952.

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1. Wolfson, W. Q.: Mississippi Valley M. J. 77: 66, 1955.

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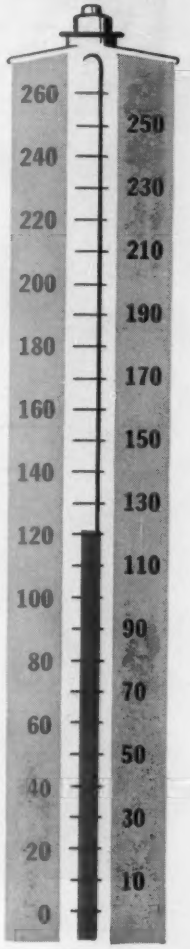

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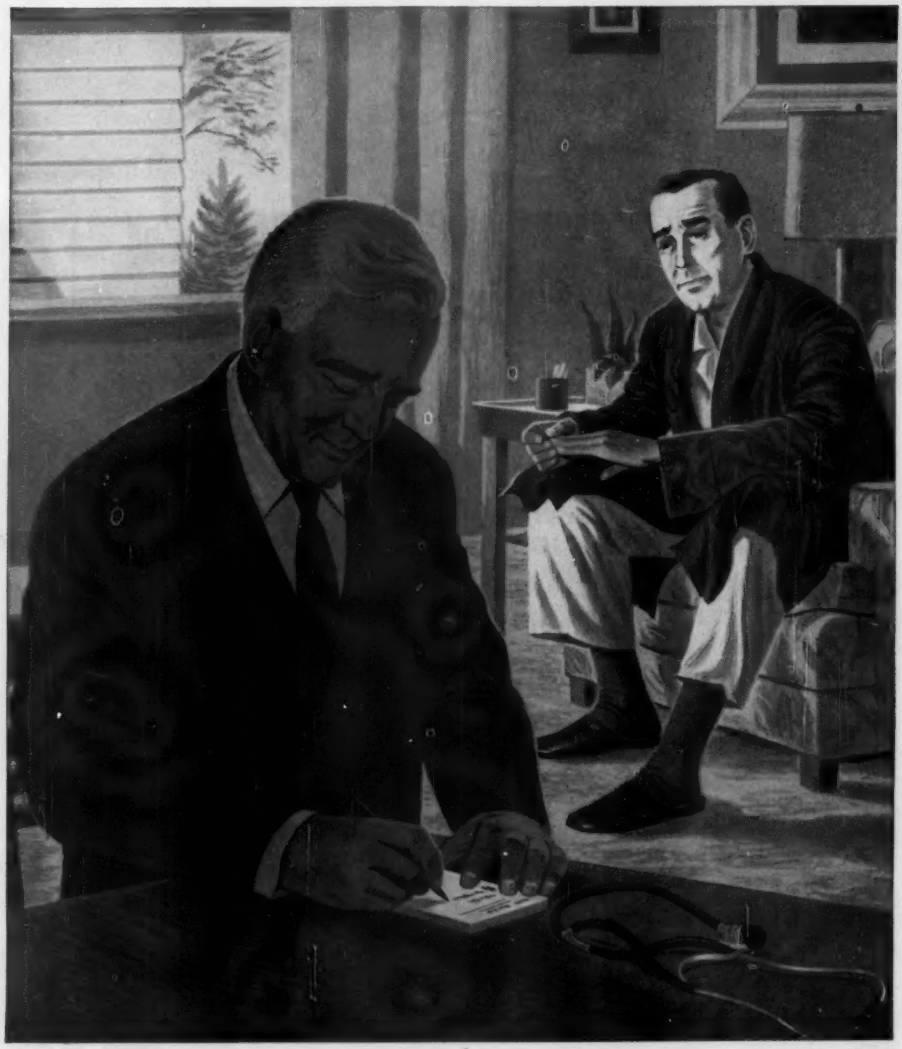

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1. Cass, L. J. and Frederik, W. S.: Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation. Journal-Lancet, 73:414 (Oct.) 1953.

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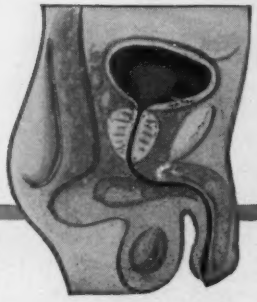

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TYPE-SPECIFIC COLD AUTO-ANTIBODIES AS A CAUSE OF ACQUIRED HEMOLYTIC ANEMIA AND HEMOLYTIC TRANSFUSION REACTIONS: BIOLOGIC TEST WITH BOVINE RED CELLS *

By A. S. WIENER, F.A.C.P., *Brooklyn, N. Y.*, L. J. UNGER, *New York, N. Y.*, L. COHEN, and J. FELDMAN, *Brooklyn, N. Y.*

THE purpose of this report is to describe an unusual example of acquired hemolytic anemia in which cold auto-antibodies of extremely high titer were detected in the patient's serum. While similar cases have occasionally been reported in the past,[1, 2, 3, 4, 5, 6] the one to be described here exhibited certain important differences having fundamental significance. Previous experience had shown that such patients can generally be safely transfused with any blood of the homologous A-B-O group and Rh type, provided the blood is kept warm during the injection to prevent the cold auto-antibodies from reacting with the transfused cells. The case which will be described here is unique in that severe hemolytic transfusion reactions resulted despite this precaution. The hemolytic reactions were explained when it was discovered that the cold auto-antibodies in the patient's serum were to a certain degree type-specific, and when the patient was transfused with certain rare bloods, selected by direct matching, no untoward reaction occurred. It is proposed to describe in detail the unusual features of the cold auto-antibody in the patient's serum, and the new type of blood which the antibody distinguishes. The implications of the observations for the serology of blood grouping in general will also be discussed.

CASE REPORT

The patient was a widow, 62 years of age, who was referred for treatment of a severe hemolytic anemia. When seen by us for the first time, in July, 1954, she

* Received for publication October 21, 1955.
From the Division of Immunohematology of the Jewish Hospital of Brooklyn, the Serological Laboratory of the Office of the Chief Medical Examiner of New York City, and the Blood and Plasma Bank of the New York University-Bellevue Medical Center.

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presented a clinical picture of extreme pallor without jaundice; she also complained of weakness, tinnitus, shortness of breath and palpitation. A blood count disclosed the presence of severe anemia, with a hemoglobin concentration of only 4.9 gm.%; red blood cells, 1.6 million per cubic millimeter; white blood cells, 18,750 per cubic millimeter; neutrophils, 61 (including 5 band forms); lymphocytes, 36; monocytes, 3. The blood smear showed marked rouleaux formation, with 1% reticulocytes and 1 late normoblast per 100 white blood cells. The platelets appeared normal on smear. The bleeding and coagulation times were normal, and the platelet count was 300,000 per cubic millimeter. The sedimentation rate was 150 mm./hr. by the Westergren method.

Subsequently, we obtained the following past history from Dr. Louis Segal, of Philadelphia. The patient's illness dated back to 1950, at which time a cholecystectomy had been performed. Following this the patient developed multiple lung abscesses which required surgical drainage. During a 10 week period of hospitalization she received six units of blood, five of them at a single transfusion. She stated that after the last transfusion she was told that she would "never be able to receive another transfusion." After an eight week convalescence she returned to her usual state of health and continued her work as a bookkeeper. She at no time had jaundice or highly colored urine.

In October, 1953, further studies were carried out because of the patient's anemia. At that time she exhibited marked pallor but no jaundice; she was afebrile, and there was no enlargement of liver or spleen. A blood count showed a hemoglobin concentration of 6 gm.%; red blood cells, 2.5 million per cubic millimeter; white blood cells, 11,500 per cubic millimeter; reticulocytes, 1.4%; platelets, 500,000; myelocytes, 1; metamyelocytes, 2; band forms, 16; segmented neutrophils, 23; lymphocytes, 41; monocytes, 14; eosinophils, 3, with 2 nucleated red cells per 100 white blood cells. A sternal aspiration showed an extremely active marrow, especially exhibiting increased erythropoiesis, with abundant megakaryocytes and marked erythrophagocytosis. The direct antiglobulin test on the patient's red cells was reported as strongly positive, and it was noted that the patient's serum agglutinated her own cells. The blood bank refused to provide blood for blood transfusion on the grounds that it was impossible to find a blood compatible with the patient's serum. The cold agglutinin titer was reported as positive at the highest dilution tried, namely, 1:500.

After preliminary treatment with intramuscular ACTH gel and Pyribenzamine, cautious transfusion of once-washed group O cells was tried; there was no untoward reaction, and the hemoglobin concentration rose to 9 gm.%. The patient was then placed on cortisone therapy (25 mg. three times a day), and after discharge from the hospital she returned to her regular work.

A short time later, on December 28, 1953, while working all morning in an unheated office, the patient developed a severe hemolytic crisis, with severe pains in the chest, nausea, vomiting and, finally, unconsciousness. She was taken to the hospital, transfused and placed on cortisone therapy until her hemoglobin concentration again rose to about 10 gm.%, with about 3,000,000 red blood cells per cubic millimeter. At home her hemoglobin concentration gradually fell again despite therapy, and it was in July, 1954, when she came to visit her family in Brooklyn, that this patient was first referred to us for study.

The most conspicuous abnormal finding on the blood of the patient, aside from the severe anemia, was the tendency for her blood cells to undergo spontaneous massive clumping, which made it difficult or impossible to carry out a red blood cell count. This spontaneous agglutination also interfered with the blood grouping tests, unless the blood was diluted with warm

saline solution without delay and the cells were washed in warm saline solution and resuspended before clumping had occurred. The patient's blood group proved to be A_1B MN Rh_2. It was not possible to test the patient's serum reliably for its iso-agglutinin content, because of interference from the auto-agglutinins which the serum contained. Naturally, we were skeptical of the diagnosis of group AB because of the tendency of the patient's cells to undergo spontaneous clumping. It was possible, however, to show that the patient's washed red cells were not agglutinated by group AB serum, while strong clumping occurred with anti-A and anti-B typing sera.

Preliminary tests confirmed the presence in the patient's serum of a high-titered cold auto-antibody. To demonstrate this auto-antibody, the albumin-plasma conglutination method and the antiglobulin technic proved unsatisfactory, and therefore all tests were carried out either with saline suspended unmodified red cells or with cells treated with ficin [7] and suspended in saline solution.* At refrigerator temperature, red cells from any human being, including those of the patient, both unmodified and enzyme-treated, were strongly agglutinated at the highest dilution tried in the initial tests, namely, 1:1,000. At body temperature, unmodified cells were not agglutinated, whereas enzyme-treated cells were agglutinated. Preliminary tests, using normal saline solution as diluent, showed the titer for enzyme-treated cells at body temperature to be about 300 units (the first and second tubes of the titration showed complete hemolysis of the test cells), but the patient's own cells were agglutinated to a titer of 4 units only. At the time we incorrectly ascribed the much lower titer for the patient's own cells to partial blocking or to damage to the receptors on the surface of her red cells, presumably resulting from the combination with auto-antibody in vivo. The quantitative direct antiglobulin test on the patient's cells was weakly positive, the degree of coating being only 4%. Actually, this result was probably too high, since rigid precautions were not taken to keep the red cells warm while they were being washed with saline solution.

Since the antibody in the patient's serum appeared to be nonspecific in its action, it was decided to disregard it when selecting donors for blood transfusions, especially since no agglutination occurred in cross-matching tests with unmodified cells at body temperature. For the transfusions, therefore, ordinary group AB, Rh-positive bank blood was used, but the precaution was taken to warm the blood to body temperature before transfusing it. Before each transfusion was started the patient was given 10 gr. of acetylsalicylic acid,† and the actual injection of blood generally consumed between 20 and 30 minutes. The first such transfusion, on July 29, 1954, was well

* The cell suspensions used in these tests, and all other tests described in this paper, were adjusted to a concentration of approximately 2%. The ficin used for treating the red cells was kindly provided by Merck and Company.

† The routine administration of acetylsalicylic acid at the beginning of each transfusion has proved in our hands [8] an effective method of suppressing pyrogenic reactions. This does not prevent allergic reactions or suppress the signs of hemolysis caused by incompatibility.

tolerated by the patient, and there was the expected rise in hemoglobin concentration to 6.5 gm.% (45%), with a corresponding improvement in well being. The beneficial effect lasted only a month, after which the patient returned for a second transfusion. During this transfusion the patient complained of pain at the base of the sternum, and it was then noticed that the bottle of blood felt cool to the touch, due to the failure to warm the blood adequately before the transfusion. Attempts were then made to warm the

TABLE 1
List of Transfusions Given to Patient

Transfusion Number	Date	Volume	Premedication	Reaction
1	7/29/54	500 c.c. whole blood plus 100 c.c. ACD	10 gr. acetylsalicylic acid	None. Blood count improved
2	8/24/54	Same	Same	Complained of pain at base of sternum and slight chilliness. Four hours later at home passed dark red urine
3	9/1/54	Same	Same	Complained of slight pain at base of sternum during transfusion; no other untoward reaction
4	9/22/54	Plasma removed to 500 c.c. mark	Same	None
5	10/2/54	Plasma removed to 475 c.c. mark	Same	None
6	10/4/54	Plasma removed to 425 c.c. mark	Same	None
7	10/19/54	Same	Same	None
8	11/2/54	Plasma removed to 500 c.c. mark	Same	None
9	12/8/54	Same	10 gr. acetylsalicylic acid and 10 mg. Chlor-Trimeton	Slight pain in chest; no other untoward reaction
10	12/14/54	Plasma removed to 380 c.c. mark	10 gr. acetylsalicylic acid	None
11	12/21/54	Two units of blood concentrated to 720 c.c.	Same	None
12	1/11/55	Interrupted after 200 c.c. given	10 gr. acetylsalicylic acid and 10 mg. Chlor-Trimeton	Severe chills and hemoglobinuria
13	1/26/55	Plasma removed to 400 c.c. mark	5 gr. acetylsalicylic acid and 10 mg. Chlor-Trimeton	Faintness, chills and hemoglobinuria

blood and to keep the patient warm, and the transfusion was completed. The patient felt well, but four hours later passed urine which she noticed was red. The blood count showed only half the expected rise in hemoglobin concentration.

From this point on, elaborate precautions were taken to warm the blood to body temperature and to keep the patient herself warm during each transfusion. With these precautions the next 10 transfusions were uneventful,

except that the patient complained of mild chest pain on two occasions (table 1). However, the need for transfusions appeared to be increasing in frequency, so that the patient had to be transfused as often as twice a month. During the twelfth transfusion, the transfusion had to be interrupted after 200 c.c. of blood were injected. The patient then had a severe chill and passed three samples of dark red urine containing hemoglobin. Recovery from the reaction was otherwise uneventful. The hemoglobin concentration progressively declined, to 5 gm.%, and on January 26, 1955, the thirteenth transfusion was given. Immediately after this transfusion was completed the patient complained of faintness and chills, and this was followed by hemoglobinuria. There was no anuria or oliguria, though a failure of the hemoglobin concentration to rise indicated that all the transfused cells had been destroyed. At this point the patient was hospitalized and further serologic studies were carried out in an attempt to resolve the problem.

During the preceding months a number of titrations of the cold auto-agglutinin in the patient's serum had been carried out. There are two limitations to such titrations: (1) the large intrinsic error in determining the end-point of any serologic titration, and (2) the danger of "carrying over" when titrating extremely potent antisera. To obviate the former pitfall, samples of the patient's serum obtained at different times were stored in the frozen state so that all of them could be titrated in parallel for purposes of comparison. To avoid the latter error, a 1 : 1,000 dilution of the patient's serum in saline solution was accurately prepared by diluting 0.5 c.c. of the serum to 20 c.c. with saline solution, and then 1 c.c. of this mixture was measured out with a fresh pipet and further diluted to 25 c.c. with saline solution. This 1 : 1,000 dilution was then used for the titrations, again starting with a fresh pipet. When these precautions were followed, the titer of the patient's cold auto-antibodies was proved to be remarkably constant, averaging about 50,000 units for unmodified cells and as high as 200,000 units for ficin-treated cells, in tests carried out at refrigerator temperature.

When the problem arose with the hemolytic transfusion reactions, the behavior of the antibody at other temperatures was reinvestigated. As has already been mentioned, in titrations at body temperature no agglutination occurred with unmodified red cells. It was noticed, however, that when the rack of tubes was removed from the water bath or incubator and allowed to stand at room temperature for five or 10 minutes, all the blood cells tested became strongly agglutinated except for the patient's own cells. This suggested a possible explanation for the hemolytic transfusion reactions, namely, that the transfused red cells passing through blood vessels in the patient's skin were cooled and then clumped and hemolyzed in vivo, while the patient's own cells were unaffected under such conditions. It was then decided, while the patient was in the hospital, to undertake the examination of a long series of donors to see if any had red cells reacting like the patient's

own cells at room temperature, since such donors presumably could be used safely for transfusions. At this point, the fact that the patient had group AB blood proved to be an advantage rather than a handicap, since her serum contained no interfering iso-agglutinins and could therefore be matched against red cells of any A-B-O group, while she could be treated as a universal recipient. From this time on, all individuals presenting themselves as prospective donors at the Blood and Plasma Bank of the University Hospital were screened by testing their red cells at room temperature with the patient's serum diluted 1 : 50 with saline solution.

While the project was going on, the possibility was suggested * of using animal blood for transfusing the patient. Previous studies [5] on sera containing potent cold auto-agglutinins had demonstrated that such auto-agglutinins react to a different degree with red cells from different animal species, e.g., rabbit cells are strongly agglutinated to a titer equaling that for human red cells, while the red cells of such domestic animals as the sheep, horse or cow are agglutinated only weakly and to a low titer.† Similar titrations were therefore carried out with our patient's serum against a series of animal bloods. These titrations were mostly done at refrigerator temperature. Again, rabbit cells were found to give the strongest reactions, the titer being approximately 100,000 units for unmodified red cells. Rhesus monkey blood cells were also strongly agglutinated but the titer was considerably lower, namely, about 10,000 units. The blood of horses, sheep and cows reacted only weakly at refrigerator temperature, horse cells giving the highest titer, namely, only 10 units. However, at body temperature the titers of such blood cells were about the same as at low temperature, and hemolysis occurred with the sheep red cells. It was therefore decided that if animal blood was to be used at all for transfusing this patient, cow cells would be tried, because the titer of the patient's serum against such cells was only 10 units at refrigerator temperature and only 5 units at body temperature.

At this point the blood bank reported that after testing 74 donors, one had been encountered whose red cells had failed to be agglutinated at room temperature, although strongly agglutinated, like red cells from all other individuals, at refrigerator temperature. By this time the patient had been in the hospital for five days, during which time the hemoglobin concentration had fallen from 5 gm.% to 3.8 gm.%, so that her need for blood had become desperate. The donor who had been found to be compatible in tests carried out at room temperature proved to be group B, type MN, type Rh_1rh, and when careful tests confirmed the report of the blood bank we proceeded with the blood transfusion, taking the customary precautions regarding warming

* Dr. I. B. Wexler made this suggestion in the course of a discussion with him regarding the problem.

† For his coöperation in providing samples of blood from healthy cows, horses and sheep, we wish to express our appreciation to Dr. Percival, of the Lederle Laboratories, Pearl River, N. Y.

the blood. The transfusion was tolerated by the patient without any untoward reaction, and was followed by the anticipated rise in hemoglobin concentration and an improvement in her clinical condition. Encouraged by this success, we continued the process of screening donors with the patient's diluted serum at room temperature. When the blood bank reported that it was having difficulty finding additional donors, we decided that this might be a good time to try a biologic test with cow blood.

For the transfusion, blood was drawn by vacuum into ACD solution from the jugular vein of one of the healthy cows previously tested. The red cells were washed seven times with large volumes of saline solution to remove all but traces of the bovine plasma, and the washed red cells were resuspended in an equal volume of saline solution. The patient was given 10 gr. of acetylsalicylic acid, a sample of her blood was drawn, and through the same 21 gauge needle, by syringe, 50 c.c. of the 50% suspension of bovine red cells were slowly injected. There was no immediate reaction, but after 10 to 15 minutes the patient suddenly became extremely apprehensive, had a sense of impending doom, complained of difficulty in breathing and asked for oxygen. Examination disclosed no abnormality in the heart sounds or respirations to account for her complaints. Nevertheless, oxygen was administered by face mask and 3 minims of epinephrine hydrochloride were injected subcutaneously. The patient's complaints quickly subsided and a sample of blood drawn at this time showed no evidence of hemolysis. However, this reaction discouraged us from further attempts at transfusion of bovine red cells. It may be mentioned that a sample of blood obtained from the patient one month after this test injection disclosed a fourfold increase in the titer for bovine red cells.

A second "compatible" donor was found after 1,032 blood donors had been screened. This donor belonged to group O, type N, type k and type Rh_1rh, and while the first donor had been a Caucasian, this one was a Negro. After confirmation of the observation that the donor's cells were not agglutinated by the patient's serum at room temperature, the blood was transfused uneventfully. The patient then exhibited marked improvement in strength as well as in blood count, and was discharged from the hospital.

Tests on the Relatives of the Patient: The patient had a rather large family, and the idea suggested itself that it might be possible by testing all the patient's relatives to find one or more who could be used as donors. Six siblings of the patient were available for testing, and also eight children of these siblings. The results of these tests are shown in table 2. It will be seen that all but two of the bloods gave strong reactions, and even these two were not comparable in their reactions with the blood of the patient herself or the blood of a donor who had been successfully used for transfusion.

Of interest is the large number of individuals of group AB in the pedigree, there being as many as four among the 14 relatives of the patient. This further confirms our conclusion that the diagnosis of the patient's group

as AB is correct, and that the reactions obtained in the grouping tests on her blood were specific and not due to auto-agglutination. That the A-B-O group, M-N type and Rh-Hr type have no relation to the blood factor detected by the patient's serum follows from the fact that three of the patient's relatives belonged to the same blood groups as herself but possessed the factor which she lacked.

When the search for compatible donors among the patient's relatives proved fruitless, the routine screening tests on blood donors presenting themselves at the blood bank was resumed. As shown in table 3, only five compatible donors were found among a total of more than 22,000 individuals

TABLE 2

Blood Groups of Patient's Relatives, and Reactions of Their Red Blood Cells with Her Serum

Blood of*	Blood Groups	Reaction after 1 Hour at Room Temperature with Patient's Serum Dilution			
		1:50	1:100	1:200	1:500
1st sibling ♂	A_1B MN k Rh_1Rh_2	+++	++	++	++
2nd sibling ♂	A_1B MN k Rh_2	++	++	++	+±
child ♂	A_1B MN k Rh_0	++	++	++	+±
3rd sibling ♂	A_1 MN k Rh_1Rh_2	++	++	++	+±
child No. 1 ♂	A_1 M k Rh_1Rh_2	++	++	++	+±
child No. 2 ♂	A_1 M k Rh_1Rh_2	++	++	++	++
child No. 3 ♂	A_1 M k Rh_1Rh_1	++	++	++	+±
Patient	A_1B MN Rh_2	tr.	−	−	−
4th sibling ♀	A_2 M k Rh_2	++	++	++	+±
child No. 1 ♂	O M k Rh_1Rh_2	++±	++	++	+±
child No. 2 ♀	O M k Rh_1rh	++±	++	++	+±
5th sibling ♀	—	++	++	++	+±
child ♀	A_1 M k Rh_2	+±	+±	+	−
6th sibling ♂	A_1B MN k Rh_2	+±	+±	+	−
child ♂	A_1 M k Rh_1rh	++	++	++	+±

* Tests include 6 siblings with 9 nephews and nieces. One sibling had died, and two others were alive but were not available for testing.

tested. Even when we assume that a number of compatible donors had been overlooked, in view of the necessarily perfunctory nature of the screening test, it was apparent that we were dealing with a blood factor of almost universal distribution. The A-B-O groups, M-N types, Kell types and Rh-Hr types of the five donors are given in table 3. Of interest is the observation that four of the five donors were Negroes, even though the great majority of donors tested were Caucasian and the patient herself was a Caucasian.

Before we describe the results of more detailed studies on the antibody in the patient's serum and the blood factor which it detects, the balance of the clinical history will be presented.

Following the two transfusions of compatible blood from the specially selected donors, the patient had a remission lasting about two months. By remaining indoors in cold weather and keeping herself dressed warmly, the patient was able to avoid any difficulty despite the fact that it was winter. During the remission she felt well except for pain in the back of her thigh and leg, which we attributed to sciatica.

On March 28, 1955, the patient suddenly experienced precordial and epigastric pain, and when examined was found to be jaundiced, with an elevated temperature. The question arose whether the patient had catarrhal jaundice or homologous serum hepatitis, or whether she was undergoing an acute hemolytic crisis. The fact that this occurred during a particularly severe spell of cold weather favored the last named possibility. Moreover, on questioning, the patient admitted that when she wanted to take her usual warm bath she was told that the bathroom was cold, so she took an alcohol sponge bath instead.

On her admission to the hospital the icterus index was found to be 22.8 units, but the cephalin flocculation test was found to be negative and the thymol turbidity only 0.6 unit. The patient was afebrile and comfortable, and appeared well except for extreme pallor. A blood count showed the hemoglobin to be 4.5 gm.%. The blood chemistry findings showed nothing remarkable except for the inversion of the albumin-globulin ratio, with an albumin concentration of 2.8 gm.% and a globulin

TABLE 3

Blood Groups of Five Donors Out of a Total of 22,964 with Blood Cells "Compatible" with Patient's Serum in Tests at Room Temperature

Blood of	Race	Blood Group	Position of Donor in Random Series of Screened Individuals
Patient	Caucasian	A_1B MN Rh_2	
Donor 1. G73230	Caucasian	B MN k Rh_1rh	74 of series
2. G74549	Negro	O N k Rh_1rh	1,032 of series
3. H16358	Negro	B MN k Rh_0	11,845 of series
4. H18654	Negro	O MN k Rh_2	13,416 of series
5. H22097	Negro	O MN k Rh_0	15,849 of series

concentration of 5.4 gm.%. Evidently the patient had experienced an acute hemolytic crisis. While a search for a compatible donor was instituted, ACTH and cortisone therapy was started.

A compatible donor became available within 48 hours, and a blood transfusion was carried out under the usual precautions. There was no untoward reaction, and in view of the prompt and gratifying rise in hemoglobin concentration to 7.1 gm.% the patient was discharged from the hospital. She felt well again except for the pain in her left calf, which we had attributed to sciatica.

The patient then experienced her final remission, which lasted about six to seven weeks. Then, on May 23, 1955, she suddenly became disoriented and went into a restless semicoma. The blood count showed the hemoglobin concentration to be only 3.5 gm.%, so that there evidently had been another hemolytic crisis. The mental symptoms were presumably due to intravascular clumping in the blood vessels of the brain. At this time only a single compatible donor was available whose address was known. There was no untoward reaction to the transfusion of his blood, and the hemoglobin concentration rose to 4.7 gm.%. However, there was no improvement in the cerebral signs and symptoms, and the patient finally died on the evening of May 28, 1955. Permission for autopsy was denied.

Identification of the Blood Factor Detected by the Patient's Serum

As has been pointed out, in addition to its ability to produce auto-agglutination in the cold, the patient's serum, in tests carried out at room temperature, detected a type-specific blood factor of almost universal distribution. As has already been shown, the blood factor in question is not related to the A-B-O, M-N, K or Rh-Hr blood group systems. Moreover, the practically universal distribution of the factor tends to exclude any relationship to the Lewis, Lutheran, Duffy, Kidd or P blood group systems. The question then presented itself whether the factor was identical with or related to any of the previously described high frequency blood factors, such as **U**,[9] **Tj^a**,[10] or **Vel**,[11] or the factor detected by the antibody in sera of certain individuals of group O in India.[12]

The comparison experiments were made possible through the kind cooperation of Dr. Leon N. Sussman, who provided us with anti-**Vel** serum; Dr. Philip Levine, who provided anti-**Tj^a** serum as well as **Tj**(a —) control blood; and Dr. H. M. Bhatia, who sent to us from India anti-"H" serum as well as some clotted blood of the donor "Z" from whom the antiserum had been obtained. Also included in the comparison were tests for the blood factor **U**. In view of the higher incidence of compatible donors among Negroes, the possibility of relationship to factor **U** suggested itself. As shown in table 4, however, anti-**U** serum strongly agglutinated the blood cells of one of the compatible donors used successfully for transfusion to the patient, while our patient's serum strongly agglutinated a sample of **U**-negative blood. Similarly, comparative tests excluded the presence of any relationship between the factor detected by our patient's serum and the factors **Vel**, **Tj^a**, and Indian "H". Interestingly enough, as shown in table 4, the anti-**Vel** serum failed to agglutinate the blood cells of donor "Z". If this observation is confirmed, this would indicate a relationship between the **Vel** antibody and Indian "H".*

Having established the fact that the factor detected by our patient's serum is different from any previously described blood factor in human blood, we searched for an appropriate name. The symbol **I** for the blood factor and anti-**I** for the corresponding antibody has been selected to emphasize the high degree of individuality of blood specimens failing to react with the patient's serum at room temperature. This symbol will accordingly be used in the remainder of this paper.

In view of the extremely low frequency of individuals with type i (**I** negative), the possibility suggested itself that such individuals might have in their serum antibodies similar to those present in the serum of our patient.

* In a personal communication sent by Dr. Philip Levine, he writes "in the hands of Levine and his staff, anti-Vel reacted with each of the 3 O_h bloods of the Providence family." (Cf. Levine et al.: Gene interaction resulting in suppression of blood group substances B, Blood **10**: 1100 (Nov.) 1955.)

TABLE 4

Comparison of Reactions of Patient's Serum and Other Serums Containing Antibodies for High Frequency Blood Factors

Test Cells*	Antiserum				
	Patient's	Anti-Vel	Anti-"H" (Bombay, India)	Anti-Tj^a	Anti-U
Compatible donor No. 18654	−	±±	++	++	++
Tj$^{(a-)}$	++±	++	+	−	±±
Donor "Z" (Bombay, India)	+++	−	−	++	±±
Type uu	+++	N.T.†	N.T.	N.T.	−
Random donor	+++	++	++	++	++

* All group O.
† N.T. = Not tested.

However, tests carried out on the sera of three compatible donors at room temperature failed to reveal the presence of any anti-I agglutinins, while at refrigerator temperature cold auto-agglutinins of average normal titer only were demonstrable.

VARIANTS OF THE BLOOD FACTOR I

Early in the studies it was noticed that blood specimens agglutinated by the serum of the patient differed in the intensity of the reactions. While the great majority of blood specimens gave strong reactions and were clumped by high dilutions of the patient's serum, occasional blood specimens gave reactions of intermediate intensity. In fact, blood specimens could be arbitrarily classified into a number of subgroups comparable to the subgroups of A, depending on the intensity and the titer of the reactions. In table 5 the difference in behavior of a number of selected blood specimens possessing the factor I is shown, in comparison with the blood cells of the

TABLE 5

Results of Saline Titrations at Room Temperature with Anti-I Serum, Showing the Difference in Reactivity of Blood Cells of Subgroups I_1, I_2, I_3, and i

Blood Specimen Number	Provisional Type	Serum Dilution in Saline Solution										Titer (Units)
		1:1	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1,280	1:2,560	
1	I_3	+++*	+++	++	++	++$_w$	+±	+	−	−	−	320
2	I_3	++	+±	+	tr.	−	−	−	−	−	−	20
3	I_1	+++	+++	+++	++±	++	++	++$_w$	+±	+$_s$	−	1,600
4	I_2	+++	++	++	++	+±	+±$_w$	tr.	−	−	−	240
5	I_3	++$_w$	+±	+$_s$	±	−	−	−	−	−	−	25
6	I_1	+++	+++	+++	+++	++	++	++	++	++$_w$	+±	5,000
7	I_2	+++	+++	++$_w$	++$_w$	++$_w$	+	−	−	−	−	160
8 Compatible donor	i	−	−	−	−	−	−	−	−	−	−	0
9 Patient	i	±	−	−	−	−	−	−	−	−	−	0

* The strength of the reactions is indicated by the number of pluses, +++ being the strongest possible reaction—one large clump.

patient and those of a compatible donor. The extremely rare individuals with blood cells compatible with the patient's serum in tests carried out at room temperature have been assigned the designation type "i" (**I** negative), while individuals with incompatible blood cells are classified as type "I" (**I** positive). Moreover, individuals of type I may be further subclassified, more or less arbitrarily, as I_1, I_2, I_3, etc., depending on the intensity and the titer of the reactions obtained.

It will be seen that the difference between a typical **I**-positive blood (titer, 1,600–5,000 units) and **I**-negative blood is at least as striking as the difference demonstrable between group A and group O blood cells, when the tests are carried out with very potent anti-**A** reagents. Similarly, the difference among the subtypes I_1, I_2, I_3, etc., is at least as striking as the difference among the subgroups A_1, A_2 and A_3 of group A blood.

TABLE 6

Results of Titrations of Patient's Serum at Body, Room and Refrigerator Temperatures against a Selected Series of Blood Specimens

Blood Specimen Number	Provisional Type	Titer (Units)* at 37° C.		Titer (Units) at 24° C.		Titer (Units) at 4° C.	
		Unmodified Cells	Ficinated Cells	Unmodified Cells	Ficinated Cells	Unmodified Cells	Ficinated Cells
1	I_2	0	25*	320	2,500	100,000	320,000
2	I_3	0	5	20	2,200	50,000	190,000
3	I_1	0	140	1,600	3,200	130,000	500,000
4	I_2	0	5	240	1,600	80,000	250,000
5	I_3	0	0	25	960	40,000	190,000
6	I_1	0	2,000*	5,000	20,000	320,000	500,000
7	I_2	0	10	160	1,900	80,000	190,000
8	i	0	0	0	120	4,000	64,000
9 Patient	i	0	0	0	240	∞†	80,000

* The titer in units is the reciprocal of the highest serum dilution giving a distinct (1-plus) reaction.

† Spontaneous cold auto-agglutination.

NATURE OF THE ANTI-I AGGLUTININ

In order to throw further light on the nature of the anti-**I** agglutinin in the patient's serum and the blood factor which it detects, comparative titrations were then carried out on red blood cells of type I_1, I_2, I_3 and i at body temperature, room temperature and refrigerator temperature. These titrations were carried out not only with unmodified red blood cells, but also with red cells treated with the proteolytic enzyme ficin (cf. table 6).

As was to be expected, the highest titers were obtained at refrigerator temperature both with unmodified cells and with ficinated red cells. In fact, the titers obtained with this patient's serum are the highest obtained with any antiserum tested by the authors to date among tens of thousands of titrations carried out during the past few decades. In tests at refrigerator temperature on the unmodified red cells of the patient herself, no end-point could be obtained because of spontaneous cold auto-agglutination, and this

is indicated by the infinity sign in the protocol. Interestingly enough, when the patient's red cells were ficinated a definite end-point could be obtained even in titrations carried out at refrigerator temperature. It will be noted that the titers obtained at refrigerator temperature were not the same for blood cells from different individuals, the titer values ranging from 4,000 to 320,000 units. With ficinated cells the titers were somewhat higher, and ranged from 60,000 to 500,000 units. Although blood cells of different subtypes, I_1, I_2 and I_3, gave correspondingly different titers, and blood of type i gave the lowest titer, it would be difficult to make a reliable diagnosis by tests carried out at refrigerator temperature alone.

Contrasting results were obtained in tests carried out at body temperature. Under these conditions, unmodified saline-suspended red cells failed to be agglutinated by the patient's serum, even undiluted. When the cells were ficinated, on the other hand, in most cases (type I_1) strong reactions were obtained, with titers ranging as high as 2,000 units. Blood of type i gave negative reactions even when ficinated. Ficinated blood of type I_2 gave reactions of intermediate intensity, while ficinated blood of type I_3 gave negative or doubtful results.

The most interesting results were obtained at room temperature, as has already been pointed out. In tests on unmodified cells at room temperature the difference between **I**-positive blood cells and **I**-negative blood cells was very sharp, as was the difference among the subtypes I_1, I_2, and I_3. When the blood cells were ficinated, in tests carried out at room temperature, clumping occurred with blood cells of all individuals, including the patient herself; but there were differences in titer values, depending on the type of the test cells, similar to the differences obtained in tests at refrigerator temperature.

The question then presented itself whether the patient's serum contained two distinct antibodies, one the anti-**I** agglutinin, the second an auto-agglutinin equally reactive for all human red blood cells. If two antibodies were present, it should be possible to separate them by absorbing the serum with the patient's own cells or blood cells of type i. In the initial experiment the absorptions were carried out with the patient's own red cells. The patient's cells first had to be washed with warm saline in order to elute any adsorbed auto-antibody, and the washed packed red cells were used for the absorption. After the absorption the red cells were washed with warm saline again to elute the absorbed antibody and then were used again for additional absorptions. This technic proved unsatisfactory, so blood was obtained from a type i donor which did not have to be utilized a second time. Absorption tests carried out with this blood in an attempt to separate a type-specific **I** antibody from the auto-antibody were unsuccessful, since while the titer for the **I**-negative absorbing cells was reduced, the titer for **I**-positive cells was reduced proportionately. Thus, the serum of the patient appeared to contain a single cross-reacting antibody having different avidities for blood cells from different individuals.

In this respect the antibody in our patient's serum is comparable to certain agglutinin extracts from beans, which react intensely with A_1 cells, only feebly with A_2 cells, and hardly at all with group B and group O cells. Attempts to separate a "pure" anti-A_1 reagent from such bean extracts by absorption have been unsuccessful,[6, 13] indicating that the reactions of such bean agglutinins (designated lectins by Boyd)[13] are due to a single uniform globulin molecule with antibody-like properties, but reacting with different avidities with red blood cells of different A-B-O groups and subgroups. Similarly, the antibodies in our patient's serum are apparently of but a single specificity, but react most intensely with type I_1 cells and least intensely with I-negative (or type i) cells. The difference in intensity of the reactions for type I_1 and type i blood cells, however, is considerably greater than the difference in intensity in the reactions of bean lectins or anti-A_1 reagents prepared from human serum for cells of subgroups A_1 and A_2.

Clinical Significance of Cold Autoantibodies and Anti-I Agglutinins

As has been pointed out in a previous paper,[4] acquired autohemolytic anemia comprises two distinct serologic entities or diseases. In one form the nonspecific antibodies in the patient's serum react most intensely at body temperature and resemble Rh antibodies in their ability to coat the patient's cells and thus give rise to a positive direct conglutination and antiglobulin reaction.[14, 15] This more serious form of autohemolytic anemia is presumably due to specific autosensitization of the patient to her (most of these patients are female) own red cells. According to Ehrlich's concept of horror autotoxicus or Felton's [16] more modern concept of immunologic paralysis, the body should be incapable of producing such auto-antibodies. However, in certain rare individuals with an abnormal capacity to produce antibodies, namely, those subject to lupus erythematosus,[15, 17] this protective mechanism does not obtain.

In the second form of autohemolytic disease, antibodies reacting most intensely or exclusively at low temperatures are formed. These resemble the natural cold auto-antibodies except for their higher titer, which in extreme cases permits the reactions to take place in vitro at room temperature, or even, in extremely rare cases, at body temperature. These antibodies we believe to be of heteroimmune origin.[4, 18] For example, in such infections as atypical virus pneumonia, and occasionally in infectious mononucleosis, antibodies are formed, presumably directed against the invading virus, which cross-react with an agglutinogen in the individual's own red cells. These cross-reacting antibodies, which may be compared to skeleton keys, have therefore only a relatively low avidity for human red cells, so that at body temperature thermal agitation causes the antigen-antibody combination to dissociate, with resulting reversal of the agglutination. Such antibodies would be expected to be far less harmful than warm auto-antibodies, and in

such cases the direct conglutination test and direct antiglobulin test, if carried out carefully on the patient's cells washed with warm saline, are generally negative.* The case described in this paper falls into this category. We believe that the natural cold auto-antibodies are also of heteroimmune origin, as a response either to some ingredient of food or to microörganisms responsible for inapparent or manifest infections.[18]

The idea suggested itself that in other similar cases of autohemolytic anemia due to cold auto-antibodies, the antibodies present might exhibit a preferential reactivity for I-positive cells. Unfortunately, no comparable case was available, but we did have serum which had been stored in the frozen state that had been obtained before death from one of our earlier patients.[5] Parallel tests were carried out with this serum and anti-I serum on selected blood cells and the results are given in table 7. The results, though not entirely convincing, suggest that the serum of our previous

TABLE 7

Comparison of the Reactions of Cold Auto-antibodies from Two Different Patients with Acquired Hemolytic Anemia

Test Cells	Titer at Room Temperature of Serum from Patient Described in this Report		Titer at Room Temperature of Serum from a Different Patient (Group A), Studied Previously	
	Unmodified Cells	Enzyme-Treated Cells	Unmodified Cells	Enzyme-Treated Cells
I_1 (group O)	5,000	20,000	32	320
I_1 (group O)	1,600	3,200	3	160
I_2 (group O)	25	960	0	15
I_2 (group O)	20	2,200	0	60
i (group B)	0	120	—*	14‡
i† (group AB)	0	240	—*	10‡

* Positive because of group incompatibility.
† Patient of this report.
‡ These reactions were presumably due to the anti-B iso-antibody in this patient's serum.

patient did indeed have preferential reactivity for I-positive cells. If further studies show that other similar cases of acquired hemolytic anemia due to cold auto-antibodies behave similarly, this could provide a partial explanation for the rareness of this condition, since presumably only I-negative individuals, who are quite rare, would be apt to produce such antibodies.

As has been shown above, the cross-reacting auto-antibody in the patient's serum reacts least intensely with the patient's own cells. Recently a number of reports have appeared of patients with acquired hemolytic anemia due to warm auto-antibodies, in which antibodies were said to have been eluted from the patient's own cells or found free in the patient's serum, which had a preferential reactivity for the patient's own cells. Thus, cases [19, 20, 21] have been reported of patients of type Rh_1rh whose serum was

* The situation may be complicated because of the existence of cases with both warm and cold auto-antibodies.[19]

said to contain antibodies, anti-**rh′** and anti-**hr″** specific for blood factors present in the patient's own blood cells. One is impressed particularly with the remarkably high percentage of cases supposedly having auto-antibodies of specificity anti-**hr″**, considering that this antibody is hardly ever produced by individuals of type Rh_2Rh_2 who lack the **hr″** factor, even after repeated transfusions of **hr″**-positive blood. The authors of these reports apparently were not impressed by this paradox, and did not realize that such peculiar observations might be challenged by other more critical workers.[22, 23]

Recently, we have had the opportunity to study a case of acquired hemolytic anemia which seems to support, but only in part, the reports cited above. Our patient was found to belong to type Rh_1rh, the presence of the **rh′** factor in her blood being established by the use of a pure anti-**rh′** serum, not containing any anti-$\mathbf{Rh_0}$ blocker. Her serum contained an auto-antibody reacting at body temperature with all ficinated human red cells tested including her own cells. At the peak of her illness, the patient's fresh serum hemolyzed ficinated red cells, while the inactivated serum produced strong clumping. Titrations revealed that test cells containing the **rh′** factor, including the patient's own cells, reacted more intensely and to a higher titer than cells lacking the **rh′** factor, the average difference in titers being about three twofold dilutions. Cells of type Rh_2Rh_2 reacted with the patient's serum like other cells lacking the **rh′** factor. When the patient's serum suitably diluted was used as a reagent, blood containing the **rh′** factor could generally be distinguished from blood lacking the **rh′** factor, but the results were not consistent. Perhaps it was reactions produced by auto-antibodies like this one exhibiting partial type specificity that has been interpreted by other workers as evidence for the presence of *absolutely* specific anti-**hr″** and anti-**rh′** in the serum of patients with acquired hemolytic anemia.

Analogy Between Acquired Autohemolytic Anemia and A-B-O Hemolytic Disease

As has just been pointed out, acquired autohemolytic anemia actually comprises two distinct immunologic blood diseases, one caused by auto-antibodies of homologous or autologous origin (truly auto-immune, with warm auto-antibodies), and the other caused by auto-antibodies of heterologous origin (heteroimmune, with cold auto-antibodies).[24] The confusion which prevails at the present time regarding the pathogenesis and treatment of A-B-O hemolytic disease is probably due mainly to the failure to appreciate that this blood disease of the newborn also comprises two distinct immunologic entities.[8, 25]

As is well known, according to Landsteiner's rule those iso-agglutinins are regularly present in the plasma the corresponding blood factors of which

are absent from the red cells. Natural iso-antibodies appear to be of heteroimmune origin [18] and, like the natural cold auto-antibodies, react more intensely at lower temperatures, although iso-antibodies generally also react at body temperature. These iso-antibodies may pass through the placenta into the circulation of the fetus in utero, but generally are of too low titer and avidity to produce disease, even though the blood cells of the fetus belong to an incompatible group. When the titers of the natural iso-antibodies are exceptionally high, however, a mild hemolytic disorder may result which, in contrast to typical erythroblastosis caused by Rh sensitization, often affects the first-born incompatible baby of the family. The heteroimmune origin of the antibodies is further demonstrated by the tendency of the antibodies of the mother to exhibit a broad cross-reactivity, viz., to be of specificity anti-**C**.[26, 27, 28] Since such **C** antibodies can be produced only by individuals of group O, this mild disorder is generally restricted to babies with mothers belonging to group O.[25, 29]

In the second, more severe form of A-B-O hemolytic disease, the antibodies responsible appear to be of iso-immune origin. In most cases, whenever the cells from a group A baby enter the circulation of a group O mother, the natural iso-antibodies quickly eliminate the incompatible cells from the maternal circulation before immune iso-antibodies can be formed.* This is the same protective mechanism which tends to prevent the formation of Rh antibodies when an Rh-positive fetus has an A-B-O group incompatible with that of its Rh-negative mother. In rare cases, however, leakage of fetal blood into the maternal circulation may give rise to group-specific iso-immunization, so that subsequent babies of an incompatible A-B-O group may be typically erythroblastotic. In this variety of A-B-O hemolytic disease, manifestations tend to be more severe, so that such babies often require treatment by exchange transfusion.[25]

The two different forms of the A-B-O hemolytic disease can be distinguished first by the clinical history, since in the milder, more common form (**C** sensitization) the first-born incompatible baby is often affected, whereas in the more severe form, as in typical erythroblastosis caused by Rh sensitization, the first-born incompatible baby generally escapes. In the milder form of the disease, moreover, even though the baby belongs to group A, the serum from his group O mother may have as high a titer for B cells as for A cells (due to the presence of anti-**C**). In the more severe form, on the other hand, the titer of the maternal serum for red cells of the affected baby's group is generally much higher, because in such cases large amounts of specific anti-**A** have been formed, as well as perhaps some anti-**C**. Further studies must be done on these rarer severe cases to determine whether the red cells of affected babies give a distinct positive direct conglutination and antiglobulin reaction.

* Iso-immunization takes place regularly, on the other hand, after inadvertent transfusions of blood of an incompatible group, due to the large volume of blood injected.[6, 30]

Summary and Conclusions

A unique case of acquired hemolytic anemia is described in which the patient's serum contained cold auto-antibodies of extremely high titer. This patient was transfused successfully with warmed blood of her own group, but eventually had violent hemolytic transfusion reactions. These were explained when the patient's serum was shown to give type-specific reactions in tests carried out at room temperature. The factor detected by the patient's serum has been designated the **I** factor, and was found to be of almost universal distribution. Among 22,000 random donors, only five were found to be **I**-negative, so that their blood could be safely used for transfusion. Because of the difficulty of obtaining a compatible donor for the patient, a biologic test with bovine red cells washed thoroughly with saline solution was tried. No hemolysis resulted from the test, but an anaphylactoid reaction discouraged us from further experiments along such lines.

Further studies showed the **I** factor to be unrelated to the A-B-O, M-N, Rh-Hr and Kell systems, and to be different from other high frequency blood factors, viz., **U**, **Tj^a**, **Vel** and Indian "H".

The results of titrations of the anti-**I** agglutinin at body, room and refrigerator temperatures against unmodified red cells and cells treated with the proteolytic enzyme ficin are presented. At refrigerator temperature, potent cold auto-antibodies were demonstrated. The most striking effect was obtained at room temperature with unmodified cells, since the titers for **I**-positive cells ranged as high as 5,000 units, while there was no—or hardly any—reaction for **I**-negative cells. Reactions were also obtained indicating the existence of subgroups I_1, I_2, I_3, etc., analogous to the subgroups of A. Attempts to separate by absorption the anti-**I** agglutinin from the cold auto-antibodies were unsuccessful, indicating that a single cross-reacting antibody was involved, as in the group-specific reactions obtained with bean agglutinins.

It is pointed out that acquired hemolytic anemia comprises two distinct immunologic entities. In one the antibodies are of iso-immune origin and have properties similar to those of Rh antibodies. In the second variety the antibodies appear to be of heteroimmune origin and react best at low temperature, as in the case described in this paper. Evidence is presented which suggests that this variety of the disease may occur chiefly in **I**-negative individuals. It is suggested that, similarly, A-B-O hemolytic disease comprises two analogous, distinct immunologic diseases. The practical implications of these findings and concepts are discussed.

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Summario in Interlingua

Un caso unic de acquirite anemia hemolytic es describite. Le sero del patiente contineva auto-anticorpores frigide de altissime titros. Transfusiones de sanguine calide del gruppo del patiente succedeva, sed post alicun tempore il habeva violente reactiones transfusional hemolytic. Iste reactiones se explicava quando il esseva constatate que le patiente exhibiva typo-specificitate in tests executate al temperatura normal del interior. Le factor detegite per le sero del patiente esseva designate como factor **I**. Il esseva constatate que illo ha un distribution quasi universal. Inter 22.000 donatores non-seligite, solmente cinque esseva identificate como **I**-negative de maniera que lor sanguine poteva esser usate pro transfusiones sin risco. A causa del difficultate de obtener compatibile donatores pro le patiente, un test biologic esseva executate con erythrocytos bovin intensemente lavate in solution salin. Nulle hemolyse resultava del test, sed un reaction anaphylactoide influentiava nos a non continuar nostre experimentos in iste direction.

Studios additional monstrava que le factor **I** non esseva relationate al systemas A-B-O, M-N, Rh-Hr, e Kell e etiam que illo esseva differente de altere factores sanguinee de alte frequentia, i.e. de **U**, **Tj^a**, **Vel**, e "H" indian.

Es presentate le resultatos de titrationes del agglutinina anti-**I** al temperatura del corpore, al temperatura normal del interior, e al temperatura del refrigerator, contra non-modificate erythrocytos e contra cellulas tractate con le enzyma proteolytic ficina. Al temperatura del refrigerator potente auto-anticorpores frigide esseva demonstrate. Le plus frappante effecto esseva obtenite al temperatura normal del interior con cellulas non-modificate: le titros pro cellulas **I**-positive attingeva maximos de usque a 5000 unitates, durante que il habeva nulle (o quasi nulle) reaction pro cellulas **I**-negative. Esseva etiam obtenite reactiones indicante le presentia de sub-gruppos I_1, I_2, I_3, etc., analoge al sub-gruppos de A. Nulle successo esseva obtenite in le essayo de separar per absorption le agglutinina anti-**I** ab le auto-anticorpores frigide. Isto indicava que un sol anticorpore a reaction reciproc esseva involvite, como es le caso in le reactiones gruppo-specific obtenite con agglutininas ab fabas.

Es signalate que acquirite anemia hemolytic comprende duo distincte entitates immunologic. In le un le anticorpores es de origine immun homologe e ha characteristicas simile a anticorpores a Rh. In le secunde varietate le anticorpores es apparentemente de origine hetero-immun e reage melio a basse temperaturas, como esseva le caso in le patiente hic describite. Es proponite le conclusion que morbo hemolytic A-B-O comprende similemente duo analoge morbos immunologic distincte. Nos discute le implicationes practic de iste constatationes e conceptos.

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PSEUDOHEMOPHILIA: REPORT OF 13 NEW CASES AND STATISTICAL REVIEW OF PREVIOUSLY REPORTED CASES *

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PSEUDOHEMOPHILIA is a hemorrhagic disorder which, occurring in either sex, is distinguished essentially by a bleeding tendency and by the single laboratory abnormality of a prolonged bleeding time. The clotting time, platelet count and prothrombin time are normal, and clot retraction is usually normal. The tourniquet test is positive in about half of the patients with this disease. Though often occurring sporadically, pseudohemophilia is familial in a high percentage of cases.

Interest in this hemorrhagic diathesis was stimulated a quarter of a century ago by von Willebrand's reports [1-3] in which he described a bleeding tendency observed in 16 female and seven male members of one family on the Aland Islands near Finland. Since then, similar patients have been reported under a multiplicity of names, including pseudohemophilia, von Willebrand's disease (constitutional hereditary thrombopathy),[4-16] thrombocytic dystrophy,[17, 18] thrombasthenia,[19] capillaropathy,[20] thrombocytopathic purpura [21, 22] and athrombocytopenic purpura.[23]

In 1946 Estren, Médal and Dameshek [19] reported 11 new cases and presented a critical analysis of 62 others found in the literature since 1900. We have found 113 additional cases in the literature.[4-18, 20-22, 24-45] Another 13 patients, who have been seen at the University of Virginia Hospital, bring the total to 199.

The cumulative data on all of these cases are being presented in an attempt at better characterization of the disease. Perhaps, in view of the progress in understanding of clotting mechanisms, these data will help to determine whether pseudohemophilia is a definite clinical entity.

In deciding whether a patient with recurrent episodes of abnormal bleeding should be classified as a case of pseudohemophilia we have used, in general, the criteria followed by Estren, Médal and Dameshek.[19] The bleeding time (Duke) has been considered as abnormal if greater than five minutes on one or more occasions. In most of the cases the bleeding time was usually much longer than five minutes. Clotting time (Lee and White) up to 15 minutes has been accepted as normal and, except in rare instances, the patients had clotting times below this limit. The platelet count was usually well above 150,000 per cubic millimeter. Some individual cases

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in several of the reported series [7, 29, 34, 44, 46–49] had certain features of pseudohemophilia but have been omitted from our analysis because some of the data failed to meet these criteria or were inadequate for classification.

Clinical Course

The disorder usually becomes manifest in childhood, often within the first few weeks of life.[7, 8, 22, 25, 29, 31, 33, 35, 37, 38] The incidence in the two sexes is about equal. Most patients give a history of having "always" had a tendency to bleed excessively, but in a very few the initial manifestation has not appeared until after the age of 40.[44] In childhood, growth and development are normal, as a rule, despite recurring episodes of bleeding. Spontaneous bleeding except from the nose and gums is uncommon, but minor abrasions and trauma often produce excessive bleeding, ecchymoses and hematomata. Loss of deciduous teeth, therapeutic injections and even bee stings may be followed by serious bleeding. Hemarthrosis [13, 26, 30, 33, 34, 38] and hematuria occur in only a small percentage of patients.

Despite these troublesome episodes, prognosis for life appears to be relatively good. In males the hemorrhagic episodes often decrease in frequency and severity with increasing age.[7, 8, 29, 34] In females the clinical manifestations may become more severe after puberty because of menorrhagia and metrorrhagia. Menstruation at times lasts for several months, but in the same patient at other times is entirely normal. Pregnancy is an added hazard. It commonly terminates in a spontaneous abortion or as a term delivery complicated by severe and prolonged postpartum hemorrhage.[8, 16, 19, 29, 33, 38, 39] Yet we have found no report of maternal death during pregnancy or in the postpartum period. One of our patients (case 4) survived three full term pregnancies and a cesarean section. Case 12 had three normal pregnancies, and two others had single normal pregnancies. Others [16, 38] have reported instances of uncomplicated pregnancy and delivery. These same patients at other times have had pregnancies that were associated with spontaneous abortion or serious postpartum hemorrhage.

As is the case with most other individuals, patients with pseudohemophilia at some time during their lives face the prospect of dental extractions and surgical operations. All such procedures are major hazards for these patients. There is great variability in the bleeding tendency in a given patient from time to time, and the probability of the occurrence of hemorrhage cannot be predicted by a review of his past history or the laboratory tests. The bleeding tendency does not always parallel the bleeding time.[8, 19, 27, 33] Patients who have gone through major operations without hemorrhage may bleed severely at a later operation.[8] The reverse sequence may likewise occur (case 7). Despite the prolonged hemorrhage that often occurs, only one death from postoperative hemorrhage has been reported [19] in a patient with pseudohemophilia. This fatality followed splenectomy.

Five other reported cases have survived this operation,[8, 19] and several have survived hysterectomy.[19, 33, 39, 45] The 13 patients in our series have survived two tonsillectomies, a hemorrhoidectomy, an appendectomy, a perineorrhaphy, a cesarean section, a craniotomy for subdural hematoma, polypectomy (12 times in one patient), two circumcisions, three uterine curettages and a hysterectomy. Sixty-six of the 199 reported cases have had excessive bleeding after dental extractions or loss of deciduous teeth.

The vast majority of patients survive their bleeding episodes without permanent or incapacitating deformity. The incidence of the various bleeding manifestations that have occurred is shown in table 1. Only four deaths from hemorrhage have been reported in the 199 cases in which the available clinical and laboratory data were considered adequate for the diagnosis of pseudohemophilia. Death in these patients followed epistaxis,[33] oral hemorrhage,[7] cerebral hemorrhage,[19] and postsplenectomy hemorrhage.[19] The family histories include reports of death from hemorrhage in 37 relatives of patients studied,[7, 17, 22, 26, 29, 33, 37, 38, 39, 40, 49] but one cannot determine how many of these relatives had pseudohemophilia. This uncertainty renders more difficult the determination of prognosis in the disease. Certainly many of the patients survive beyond middle age. Of the 172 patients whose ages were listed, 45 were in their first decade, 67 between the ages of 10 and 30 years, 44 between the ages of 30 and 50 years, and 16 above the age of 50. The three oldest were 77, 75 and 73 years of age.

Pathogenesis

Hemorrhagic disorders may be the result of a deficiency of plasma constituents, a vascular abnormality, or a platelet defect. In pseudohemophilia, plasma factors such as prothrombin, calcium, fibrinogen and vitamin C have been found to be normal almost invariably.[4, 6–8, 11, 13, 19, 22, 31–33, 38, 44, 45] In the few cases that had a deficiency in any one of these factors its correction did not correct the bleeding tendency or the bleeding time.

MacFarlane [28] in 1941 attributed the abnormal bleeding in this disorder to a capillary defect, after demonstrating by direct visualization that the nail-bed capillaries in patients with pseudohemophilia appeared bizarre and distorted and failed to constrict normally after puncture. Similar capillary abnormalities have been reported subsequently.[26, 27, 29, 40, 49] Other authors,[10, 15, 19, 24, 32, 37] who employed variations of MacFarlane's technic, have found only normally appearing capillaries in the few patients so examined. Jamra and associates [20] studied the capillaries in patients with pseudohemophilia and in normal subjects. They applied stimuli that varied from a simple needle prick to perforation of the capillary, with the production of local hemorrhage, and concluded that no difference existed between the normal pattern and those seen in these "constitutional capillaropathies." They emphasized that capillary irregularities occur even in normal subjects. As

further evidence of local vascular defects in pseudohemophilia, Quick [50] has cited Roskam's observation that in one of his patients a bleeding time was three minutes in one ear and 48 minutes in the other. A similar situation was found in our case 13: the bleeding time was 17½ minutes in the left ear and, on the same occasion, 180 minutes in the right. Another test of capillary function, capillary fragility as measured by the tourniquet test, is not regularly abnormal in pseudohemophilia. The tourniquet test was

TABLE 1

Hemorrhagic Symptomatology in 199 Cases (95 Males and 104 Females) of Pseudohemophilia (Authors' Cases Plus Cases from the Literature). Number of Patients in whom Each Type of Bleeding Occurred

Symptom or Finding	Male		Female	
	Number	Per Cent	Number	Per Cent
Epistaxis	70	73	67	64.5
Ecchymoses, or easy bruising	53	55.5	70	67
Abnormal menstrual bleeding	0	0	53	51
Excessive hemorrhage from minor cuts, abrasions or trauma	35	37	35	33.5
Gingival or oral bleeding	31	33	37	36
Excessive bleeding after dental extraction or loss of milk teeth	27	28.5	38	36.5
Postoperative hemorrhage	18	19	21	20
Petechiae	15	16	18	18.5
Upper gastrointestinal hemorrhage	16	17	6	6
Hemarthrosis	12	12.5	5	5
Postpartum hemorrhage	0	0	11	10.5
Genital bleeding (not inclusive of menstrual abnormalities, postpartum hemorrhage or bleeding after circumcision)	1	1	8	7.5
Hematomata	8	8.5	8	7.5
Lower gastrointestinal hemorrhage	7	7.5	3	3
Hematuria	7	7.5	2	2
Bleeding from venipuncture, injection site or insect sting	5	5	2	2
Meningeal or intracranial hemorrhage	3	3	1	1
Hemoptysis	2	2	2	2
Bleeding from ear	2	2	1	1
Umbilical hemorrhage	2	2	0	0
Retinal hemorrhage	1	1	1	1
Site not listed	3	3	6	6
Total	318		395	

positive in 54.3% of the cases analyzed in which the test was reported. Petechiae were reported in only 16.6% of cases.

As another explanation of the abnormal bleeding in this disease, a qualitative platelet deficiency has been postulated. Even in the few patients with pseudohemophilia in whom the platelet count was at times borderline or low,[7, 8, 19] there was no correlation between the number of platelets and the bleeding time or the tendency to bleed. Von Willebrand and Jürgens [8] believed the disease to be due to poor agglutinability of the thrombocytes and,

by means of a "thrombometer," demonstrated this deficiency in vitro. Others [4-7, 10-12, 14, 17, 18, 21, 22, 28, 31, 35, 51] have commented on a similar lack of platelet agglutination or on the presence of abnormalities in platelet morphology and staining. Giant platelets, anisocytosis and pycnosis have been described. If agglutination of the platelets serves to seal the injured blood vessel,[50] a decreased agglutinability might affect the bleeding time. Upon agglutination and lysis the platelets are thought to release a vasoconstrictor substance.[52, 53] This latter platelet function might reconcile the opposing ideas of a vascular versus a platelet defect in pseudohemophilia. Bigelow,[53] however, has reported normal serotonin activity in the plasma of two patients believed to have pseudohemophilia.

The prothrombin consumption test [54] has been found abnormal by some authors [11-13, 15, 17, 18, 49, 51] and normal by others [22, 38, 40, 44, 45, 55] in small numbers of cases of pseudohemophilia. Five of our cases had abnormal prothrombin consumption tests and one had a normal result. Of the other cases reviewed, seven had poor prothrombin consumption and 11 normal. A decreased prothrombin consumption may represent either a deficiency of a plasma thromboplastin factor such as occurs in hemophilia states (AHG, PTC and PTA factors), or a deficiency of the platelet thromboplastin factor that occurs in thrombocytopenic purpura. In the former case the clotting time usually is prolonged and the bleeding time is normal. In the latter disorder the platelets are decreased in number, the bleeding time is prolonged, and the clotting time is normal. Sussman, Wald and Rosenthal [56] have reported an instance of a hemorrhagic diathesis in a 49 year old woman who apparently had a qualitative defect in platelets, abnormal coagulation time and deficient prothrombin consumption, associated with normal bleeding time and normal number of platelets. Bernard and others [51] offered strong evidence that the defective prothrombin consumption in pseudohemophilia represented a platelet defect, since they were able to correct the prothrombin consumption deficiency in plasma of one of these patients by the addition of isolated normal platelets. They were not able to correct the prothrombin consumption deficiency in deplateletized normal plasma by addition of the platelets or plasma from a patient with pseudohemophilia, although this was corrected by addition of normal platelets or plasma. A possibly different result was obtained by De Vries,[22] who reports that the prothrombin consumption deficiency (but not the poor clot retraction) in blood of patients with thrombocytopenic purpura was corrected by addition of blood from a patient with pseudohemophilia.

Although clot retraction was normal in the vast majority of reported cases, the patients of De Vries with pseudohemophilia had poor clot retraction, which was corrected by the addition of washed normal platelets. Pavlovsky [27] was able to correct the clot retraction of blood from a patient with thrombocytopenic purpura by the addition of platelets from a patient with pseudohemophilia who had normal clot retraction. Defective clot

retraction appears to be unusual in pseudohemophilia. Clot retraction was reported as normal in 88.5% of cases of pseudohemophilia in which results were listed. Conceivably, there could be an additional platelet defect in patients with poor clot retraction. Fonio [57] reported two structural elements of platelets, namely, hyalomere and granulomere. Clotting was said to take place in the absence of hyalomere, but only in the presence of hyalomere did clot retraction occur.

The place of heredity in this disease is difficult to evaluate. Of the 199 cases studied, a positive family history for abnormal bleeding was elicited in 126. In 55 of these cases relatives of both sexes were affected. In 18 the patient and affected relatives were all males, while in eight cases the patient and affected relatives were all females. In 45 cases the sex of affected relatives was not indicated. Von Willebrand [1-3] felt that a dominant sex-linked trait was involved. Imerslund [8, 9] cited several cases that seemed to represent a recessive character because the parents were related but had no hemorrhagic diathesis. Others [7, 27, 38, 43] have also cited cases of pseudohemophilia who had no known antecedents with a bleeding tendency but whose parents were related. The significance of a "family history of bleeding" has been very difficult to evaluate unless the individuals could be studied. One of our patients gave a history of an uncle who "bled to death from a scratch." On more careful investigation this proved to be a case of stab wound in the heart. Careful histories of various members of the families and laboratory studies of siblings, parents and other relatives might determine whether the disorder is really familial.

The studies so far reported are somewhat conflicting and suggest that not all the patients with "pseudohemophilia" have the same defect in hemostasis. It seems established that a sizable percentage of them have more than a capillary defect. Several observations point toward a qualitative defect in the platelets. These are the occurrence of a prolonged bleeding time, impaired prothrombin consumption, defective clot retraction, poor agglutination of platelets, and morphologically abnormal platelets. Certain other features, such as a variation of clinical severity and bleeding time in the same patient at different times and the defective prothrombin consumption test, suggest some similarity to thrombocytopenic purpura. The onset early in life, the chronicity of the disease, and the failure of splenectomy in reported cases suggest that if a platelet defect exists it is the result of an injury that differs from that in primary thrombocytopenic purpura in mechanism of action rather than in degree of severity. Until the pathologic physiology of the disorder and the influence of heredity are better understood one cannot say if the patients now diagnosed "pseudohemophilia" represent a single entity. They apparently differ from other recognized hemorrhagic states. But whether the patients in this group represent a disease with a common etiology, or a syndrome with a common defect in hemostasis, or an even more heterogeneous group, remains to be determined.

Diagnosis

Pseudohemophilia should be considered in the differential diagnosis of every patient with repeated episodes of abnormal bleeding. Although a prolonged bleeding time is necessary for the diagnosis, the bleeding time on any one determination may be normal. Therefore, several determinations of bleeding time should be made before the possibility of pseudohemophilia is discarded in a case in which all other laboratory findings are normal. The

Table 2

Differential Points between Pseudohemophilia and Other Hemorrhagic Diseases

	Pseudo-hemophilia	Hemophilia	Thrombocyto-penic Purpura	Vascular Purpura	Plasma Throm-boplastin Ante-cedent (PTA) Deficiency	Plasma Thrombo-plastin Component Deficiency
Bleeding time	Prolonged	Normal	Prolonged	Normal	Usually normal	Normal
Clotting time	Normal	Prolonged	Normal	Normal	Normal to 30 min.	Prolonged
Clot retraction	Usually normal	Normal	Markedly prolonged	Normal	Normal	Normal
Platelet count	Normal	Normal	Decreased	Normal	Normal	Normal
Tourniquet test	Positive in 50%	Negative	Usually positive	Positive	Usually negative	Negative
Prothrombin time (one-stage)	Normal	Normal	Normal	Normal	Normal	Normal
Prothrombin consumption	Poor in 50%	Poor	Poor	Normal	Poor	Poor
Familial	Frequently. Transmitted by either sex	Sex-linked recessive. Transmitted by female to male	May be, but usually is not	No	Yes Not sex-linked	Sex-linked recessive
Sex	Either	Male	Either	Either	Either	Male
Hemarthroses	Uncommon	Characteristic		Occasionally	Rare	
Petechiae	Rare	Usually absent	Characteristic	Rare	Usually absent	Usually absent
Hematuria	Uncommon	Common		Occasionally	Rare	Rare
Megakaryocytes in marrow	Normal in number and forming platelets		Increased in number but not forming platelets	Normal in number and forming platelets	Normal	Normal

most common conditions from which this disease must be differentiated are hemophilia and thrombocytopenic purpura. The differential features are presented in table 2.

Treatment

There is no satisfactory specific treatment for the bleeding of pseudohemophilia. Blood transfusions may be indicated because of anemia. Results from the use of fresh whole blood for the control of bleeding in these patients have been disappointing.[4, 6–8, 11, 13, 15, 22, 31–33, 38, 47] In view of the in

vitro studies of Bernard et al.,[51] it would be interesting and logical to transfuse fresh whole blood with silicone and other technics that provide, at least temporarily, serviceable platelets for the recipients. Jacobson [44] feels that cortisone is effective in the control of bleeding. Calcium,[83] rutin,[32] vitamin K,[33] vitamin C [21, 33] and snake venom [33] are other remedies that have been of little value. The natural course of the disease is so variable that it may be difficult to distinguish a good therapeutic result from a spontaneous remission. Until more is known about the nature of the disease the best management would seem to be the use of symptomatic treatment, the use of local hemostatic agents, and the avoidance of all but the most urgent surgery. The avoidance of surgery should apply even when the bleeding time is normal, once the diagnosis of pseudohemophilia has been made.

The following abstracts of cases of pseudohemophilia seen at the University of Virginia Hospital are presented in an effort to give a better picture of the course of the disease than that afforded by a compilation of symptoms and laboratory findings.

Case Reports

Case 1. A white male born February 1, 1948, suffered bruises and hematomata from trivial knocks. He had severe prolonged epistaxis at the age of 18 months, and required cautery to control bleeding from an ear prick for bleeding time determination six months later. He bled for three days from an injury to the external genitalia at the age of three years, and had a severe spontaneous nosebleed a few days later.

This patient was admitted on April 26, 1951, with active bleeding from the site of a penicillin injection in the right buttock several hours earlier. Hemorrhage was easily controlled with Gelfoam sponge. On that occasion bleeding time was 22 minutes; clotting time, 6½ minutes; clot retraction, normal; platelet count, 603,000; tourniquet test, positive; prothrombin time, 14 seconds, control, 14 seconds; prothrombin consumption, slightly reduced; bone marrow, normal.

He was followed in the Pediatric Clinic, presenting on one occasion petechiae about the eyes after crying and on another occasion scattered ecchymoses. In one interim period he had an episode of oral bleeding and a traumatic hematoma of the scalp. The prothrombin consumption test was repeated on three occasions and remained slightly abnormal. The tourniquet test was positive on four occasions. Repeat bleeding times were more than 30 minutes, more than 20 minutes, 11½ minutes, and more than 45 minutes. Clotting times were 2 minutes, 9 minutes and 7 minutes. Platelet counts were 408,000 and 139,000.

There was moderate bleeding, controlled by Gelfoam packs, following extraction of two abscessed teeth on May 12, 1953. When seen on May 14, 1954, the patient had suffered only two moderate episodes of nasal hemorrhage in the previous year, and both had responded readily to packing. At the time of this visit one small ecchymotic area was noted on the left upper arm. The bleeding time was then more than 20 minutes; clotting time, 2½ minutes; platelet count, 345,000; tourniquet test, positive; prothrombin consumption, very mildly deficient.

The family history is of interest in that the maternal grandfather and the grandfather's three brothers have a tendency to bleed excessively from minor cuts or scratches.

Case 2. A Negro male infant presented a hematoma of the left forearm at birth on October 7, 1952. Circumcision on the second day of life caused no abnormal bleeding.

The first episode of epistaxis occurred following a coughing spell on April 30, 1953, and continued intermittently until the child was admitted with profuse hemorrhage from the right side of the nose three days later. The bleeding ceased after the application of hydrogen peroxide packs and transfusion of 250 ml. of fresh whole blood. Bleeding time was greater than 15 minutes; clotting time, 3 minutes; platelet count, 175,500. On the following day the bleeding time was 5½ minutes.

After a quiescent period of 11 months, spontaneous epistaxis occurred on March 24, 1954, while the child lay quietly in bed. Cold compresses controlled the bleeding temporarily but hemorrhage recurred and, despite compresses and cautery, continued until admission on March 27, 1954. The bleeding again subsided after transfusion. Bleeding time was 7 minutes; clotting time, 4 minutes; platelet count, 159,000; prothrombin time, 14 seconds, control 11 seconds; sickle cell test, negative; tourniquet test, negative; prothrombin consumption, normal. Bleeding time on the following day was 5 minutes, and repeat prothrombin time was 13½ seconds, control 11 seconds.

There was no family history of a hemorrhagic disorder in this case. Four siblings appeared normal.

Case 3. A white male born June 16, 1950, bled for two days following circumcision at the age of 10 days and again for two days following a scratch on the finger at eight months. There was no bleeding from the site of pertussis inoculations at the age of six months. The family history revealed no hemorrhagic disorders, and the parents were not related.

When seen on March 8, 1951, because of active bleeding from the site of a penicillin injection in the right deltoid region nine hours previously, he had large ecchymoses over the left tibia and left upper arm. On that occasion the bleeding time was more than 45 minutes; clotting time, 13 minutes; prothrombin time, 17 seconds, control 13 seconds; tourniquet test, negative; platelet count, 369,000; clot retraction, normal; prothrombin consumption, markedly deficient. The bleeding time two days later was 6 minutes, while the prothrombin consumption test was still markedly abnormal. Bleeding responded but poorly to topical thrombin and pressure dressings, but gradually ceased after transfusion of 200 ml. of fresh whole blood.

The patient was next seen on April 23, 1954, with numerous purpuric lesions widely distributed over the body and with a severely swollen, ecchymotic left hand which was the site of a wasp sting two days earlier. The bleeding time was then 20 minutes; clotting time, 3 minutes; platelet count, 346,000. Since 1951 he had had frequent episodes of "bruising" or spontaneous skin hemorrhages, epistaxis, and hemorrhage resulting from slight scratches, and had received whole blood transfusions on seven occasions.

Case 4. A white female born October 16, 1903, has a lifelong history of abnormal bleeding. This included bleeding for two or three days from slight cuts and dental extractions in childhood; one episode of gross hematuria at age 22 years; frequent gingival hemorrhages before the occurrence of edentia at age 32; abnormal blood loss following perineorrhaphy 15 years ago; postpartum hemorrhage lasting approximately nine days following each of three otherwise normal pregnancies; massive hemorrhage at the onset of her last labor, in 1944, terminating in removal of a dead fetus by cesarean section; repeated menorrhagia during the last 10 years and metrorrhagia during the last two years, for which uterine curettage in October, 1953, provided no pathologic explanation.

When admitted for hematologic study on January 29, 1954, this patient presented essentially normal physical findings except for slight vaginal bleeding. Laboratory studies revealed a bleeding time of 9½ minutes, 2 minutes, 9 minutes and 9½ minutes; clotting time, 4½ minutes; clot retraction, normal; tourniquet test, negative; platelet count, 262,000, with normal morphology; prothrombin time, 14 seconds, control 13 seconds; prothrombin consumption, moderately retarded. Before the studies were

complete the patient was called home because of a family tragedy. She returned 10 days later, having had no bleeding in the interim. The bleeding time was then found to be 1½ minutes, 1½ minutes and 2 minutes; clotting time, 3 minutes and 5 minutes. She continued to have episodes of intermittent uterine bleeding. Studies done on November 10, 1954, showed a bleeeding time of 5 minutes; clotting time, 7½ minutes; clot retraction, normal; platelet count, 253,000; prothrombin consumption, normal.

The parents of this patient were not related. The mother had bled excessively after an operation several years before. An only sister died of tuberculosis at age 27 years, the terminal event being pulmonary hemorrhage. One brother has tuberculosis and has had several episodes of hemoptysis. No bleeding disorder has been noted in any of the patient's three children.

Case 5. A white housewife had bruised easily all her life, and had bled excessively from minor cuts and scratches and after dental extractions. Menses became irregular and the flow almost continuous following a miscarriage four months after her marriage at the age of 17. A pregnancy and delivery two years later were uncomplicated. Studies done at another hospital on November 19, 1952, showed a bleeding time of 4 minutes; clotting time, 3 minutes; platelet count, 158,100; prothrombin time, normal. Repeat studies on December 23, 1952, demonstrated a bleeding time of 6 minutes; clotting time, 7 minutes; clot retraction, normal; platelet count, 500,000.

Because of continued severe menometrorrhagia she was referred to this hospital for blood studies on February 27, 1953, at the age of 21. Bleeding time was then 10 minutes; clotting time, 12 minutes; clot retraction, normal; tourniquet test, positive; platelet count, 378,000. On March 17, 1953, the bleeding time was 4 minutes; platelet count, 266,000; tourniquet test, positive.

During the next year the spacing of her menstrual periods varied from three to eight weeks, the flow was always excessive, and the duration of periods from two to eight weeks. For a part of that year she took some oral medication, presumably hormonal, to which she attributed some improvement. On May 13, 1954, the bleeding time was 7 minutes; clotting time, 13 minutes; tourniquet test, negative; platelet count, 230,000, with normal morphology; prothrombin consumption, normal.

The family history was significant in that the mother, now 43 years of age, had had severe menometrorrhagia for several years. The parents are not related.

Case 6. A 13 year old white male, when seen on June 9, 1933, gave a history of spontaneous epistaxis "off and on" all his life, and had had episodes of bloody stools during the preceding 18 months. The only abnormal physical finding on his first visit was rectal polyps. Bleeding time was 2½ minutes; clotting time, 3½ minutes.

During the next 10 years he had repeated episodes of spontaneous epistaxis. He also had rectal bleeding, and benign polyps were removed from the rectum or colon on 12 occasions. On one occasion, in March, 1943, ecchymosis was noted on the left wrist. Platelet count at that time was 361,000; clot retraction, normal; clotting time, 9 minutes; tourniquet test, strongly positive; prothrombin time, 14 seconds, control 14 seconds; bleeding time, 30 minutes. (Bleeding time four days later was 5 minutes.)

In recent years his epistaxis has been less frequent and less severe than in earlier life. Although in the past he had undergone tonsillectomy, myringotomy and appendectomy without significant postoperative bleeding, this patient had profuse hemorrhage for several hours following excision of a hemorrhoid by the family physician in March, 1954. Routine laboratory studies a month later showed the bleeding time to be 3½ minutes; clotting time, 8½ minutes; platelet count, 200,000; prothrombin time, 11 seconds, control 11 seconds; tourniquet test, mildly positive.

The paternal grandfather of this patient had gastrointestinal and nasal hemorrhages. The father had had repeated epistaxis in his youth. One sister had fre-

quent epistaxis and severe hemorrhages from polyposis of the colon, although her menstrual history was normal. Two brothers were "bleeders," and one of these bled to death following tonsillectomy at age 19. His mother, two sisters, two brothers and three children have no history of abnormal bleeding. The parents were not related.

Case 7. A brother to case 1 at two years of age began having episodes of spontaneous epistaxis about once a month. When first admitted, at age three, with epistaxis, anemia and ecchymoses of the legs, he had a clotting time of 6½ minutes. The hospital course was marked by intermittent epistaxis and bleeding from the right ear, partially relieved by cold compresses.

Tonsillectomy at the age of nine was complicated by excessive bleeding. Following a trivial bump on the head at the age of 16 he developed a subdural hematoma. On this occasion the bleeding time was 7 minutes, 9 minutes and 10 minutes; clotting time, 6 minutes; prothrombin time, normal; platelet count, 1,000,000. Evacuation of the clot was followed by uneventful recovery, with no postoperative hemorrhage.

Until 1941, when he moved away from this vicinity, this patient continued to be seen for epistaxis, which responded to cold compresses and nasal packs. The family understands that he continues to be troubled by occasional mild epistaxis at the age of 38 years.

Case 8. A white female had had a tendency from early childhood to bleed copiously from slight cuts, and often noted the presence of unexplained bruises. She also had occasional nasal hemorrhages. At the ages of 15, 18 and 19 years she had profuse hemorrhages, lasting for days or weeks, after dental extractions. The menses were normal, and there was a normal pregnancy and delivery. The family history was negative for bleeding disorders.

On June 23, 1949, at the age of 20 years, she presented normal physical findings except for mild diffuse enlargement of the thyroid. The bleeding time was 8 minutes; clotting time, 12 minutes; clot retraction, normal; prothrombin time, 14 seconds, control, 13 seconds; platelet count, 250,000, with normal morphology; tourniquet test, negative.

In a recent communication the patient stated that during the last five years her bleeding tendency had seemed less pronounced. Several dental extractions during this period were followed by only moderate bleeding.

Case 9. A Negro female infant appeared normal at birth on April 16, 1946. No family history of abnormal bleeding was elicited. The subject bled for three days from a small cut on the finger at the age of five years, and bled "half a cup" after extraction of a loose tooth a short time later.

Hospital admissions are briefly summarized as follows:

January, 1952: Bleeding gums for three days after being stuck by a fish bone; gradual response to thrombin topical and 500 ml. of whole blood. Bleeding time, 12 minutes, 13 minutes and 24 minutes; clotting time, 24 minutes; clot retraction, normal; prothrombin time, 13 seconds, control, 12 seconds; platelet count, 172,000; sickle cell test, negative; prothrombin consumption, markedly deficient.

March, 1952: Spontaneous epistaxis for 24 hours; response to thrombin topical and cold compresses. Bleeding time, 37½ minutes; clotting time, 10½ minutes and 14½ minutes; clot retraction, normal; prothrombin time, 15 seconds, control, 14 seconds; platelet count, 287,000; tourniquet test, negative.

April, 1952: Bleeding from lip for 24 hours following slight trauma; response to cold compresses.

June, 1952: Bleeding from gums; gradual cessation after transfusion of whole blood. Bleeding time greater than 30 minutes; clotting time, 4 minutes; clot retraction, normal; prothrombin time, 16 seconds, control, 13 seconds; platelet count, 231,000; sickle cell test, negative; tourniquet test, negative; prothrombin consumption, deficient.

June, 1952: Bleeding around a loose tooth; response to local Adrenalin and ice, and 250 ml. of whole blood.

June, 1952: Epistaxis and bleeding from the gums, the former controlled by cautery.

December, 1952: Periarticular swelling and probable traumatic hemarthrosis of right knee.

December, 1953: Hemorrhage into tissues following crush injury to right arm. Bleeding time, 14 minutes; clotting time, 7 minutes; prothrombin time, 13 seconds, control, 13 seconds; prothrombin consumption, deficient.

August, 1954: Emergency room visits with epistaxis on three successive days. Electrocautery of bleeding point was unsuccessful. Hemorrhage was controlled with epinephrine-soaked sponge packs.

This patient was in a foster home, and her family history could not be obtained.

Case 10. A white housewife of 37 years had a lifelong history of excessive bleeding from slight cuts and scratches. Bleeding had persisted for from several hours to several days after dental extractions. Her first menstrual period lasted about three months, and subsequent periods about two weeks. She had been told on one occasion that her bleeding time was greater than 45 minutes. Surgery had been postponed because of the bleeding hazard. There was no family history of abnormal bleeding.

When referred for blood studies, on July 10, 1947, she presented essentially normal physical findings except for moderate diffuse enlargement of the thyroid. Bleeding time was greater than 10 minutes; clotting time, 10 minutes; clot retraction, normal; platelet count, 281,000; prothrombin time, 15 seconds, control, 15 seconds; tourniquet test positive. (Treatment, rutin, 60 mg. daily for a month.)

She was seen again in the office five weeks later and was noted to have a few ecchymoses. There had been no significant bleeding since the previous visit. Bleeding time was greater than 35 minutes; clotting time, 7½ minutes; clot retraction, normal; platelet count, 200,000; tourniquet test, negative. This lady later moved away, and we were unable to get a follow-up.

Case 11. A 34 year old white housewife was seen on March 2, 1950, with a five year history of menorrhagia. She had always bruised easily, and bled excessively from small scratches. She had had severe hemorrhages after uterine curettage and after a dental extraction in 1949. There was no family history of abnormal bleeding.

Bleeding time was greater than 15 minutes; clotting time, 8 minutes; clot retraction, normal; platelet count, 101,000; prothrombin time, 12 seconds, control, 12 seconds; tourniquet test, mildly positive. Studies done 10 days previously at another hospital showed essentially the same results.

She was treated with rutin and, when seen again on August 29, 1950, was continuing to have menorrhagia. Bleeding time was then 11½ minutes; clotting time, 4 minutes; clot retraction, normal; platelet count, 502,000; tourniquet test, negative. We have been unable to get a further follow-up on this patient.

Case 12. A white female born August 25, 1908, was admitted on April 4, 1952, with ecchymoses on the feet and legs and widespread petechial eruptions on the body. She had experienced similar eruptions each summer for the previous four years, and the lesions had progressed to ulcerations about the ankles. There had been no known toxic exposure, and an allergy work-up had been negative.

All her life she had noted a tendency to bruise easily, and had had occasional bleeding from the gums, especially after brushing the teeth. Hysterectomy was performed at age 31 years because of metrorrhagia. Postoperative hemorrhage was not excessive. She had had three normal pregnancies.

The patient's mother has had a tendency to bruise easily all her life. One of

three sons has had frequent severe epistaxis since infancy. The parents are not related.

In addition to the petechiae and ecchymoses, the skin of the feet and legs presented many hyperpigmented spots at the site of previous lesions. There was also some decrease in sensory perception of the feet. The right retina presented nevoid pigmentation.

Bleeding time was 10 minutes; coagulation time, 5½ minutes; clot retraction, normal; tourniquet test, negative; platelet count, 301,700; platelet morphology, normal; hematocrit, 43%; bone marrow, considered normal; "L.E." preparation, negative; prothrombin consumption, retarded.

On her return for blood studies on May 13, 1954, she had no bleeding symptoms. The petechiae and ecchymoses with ulceration of the feet had recurred last summer as previously and had subsided with the onset of cooler weather. On this visit bleeding time was 1 minute; coagulation time, 10 minutes; platelet count, 279,000; hematocrit, 41%.

Case 13. A white female in childhood bled excessively from the nose and gums and had intermittent subcutaneous hemorrhages on the face and limbs, often without obvious trauma. One brother had died in infancy of an umbilical hemorrhage, another at age 16 of intractable epistaxis, and a third, with a bleeding tendency since birth, died at age 16 of a postappendectomy hemorrhage.

This patient was first admitted on August 13, 1919, at the age of 11 years, because of bleeding gums, and was effectively treated with topical Adrenalin. In later years she had occasional epistaxis and gum bleeding, and one severe hemorrhage following tooth extraction.

Subsequent visits are briefly summarized below:

July 4, 1942: Intermittent profuse vaginal bleeding since abortion at three months stage six weeks previously. Two uterine curettages had been unavailing. Bleeding time, 12 minutes, 72 minutes, 36 minutes, 9½ minutes, 9 minutes, 10 minutes, 72 minutes, 17½ minutes (left ear), and 180 minutes (right ear on same occasion); clotting time, 2 minutes, 8 minutes, 7½ minutes, 8½ minutes; clot retraction, normal on three occasions; platelet count, 366,000; prothrombin time, 15 seconds, control, 15 seconds; tourniquet tests, negative. Eight transfusions.

August 28, 1942: Appointment for follow-up. Intermittent metrorrhagia in the interim.

May 14, 1947: Admitted for consideration of extraction of defective teeth. Gum bleeding; ecchymoses over left deltoid; hematoma over right iliac spine. Bleeding time, 20 minutes; clotting time, 21 minutes; clot retraction, normal; prothrombin time, 16 seconds, control, 16 seconds; tourniquet test, positive. Three transfusions. Dental extractions deferred on advice.

July 10, 1947: Toothache. Bleeding time, 14 minutes; tourniquet test, positive. Ungual capillaries, punctured under direct vision, showed poor retraction.

August 25, 1949; Ecchymoses about knees, thighs and arms. Bleeding time, 55 minutes; clotting time, 24 minutes; tourniquet test, positive.

December 14, 1950: Occasional menorrhagia in interim. Admitted for dental extractions. Two teeth and several root fragments extracted; moderate bleeding, controlled with Gelfoam and pressure packs. Bleeding time, 60 minutes; clotting time, 8 minutes; clot retraction, normal; platelet count, 529,000; prothrombin time, 16 seconds, control, 14 seconds; tourniquet test, positive.

May 5, 1951: Small bruised area on right ankle and petechiae on hard palate. Bleeding time, 66 minutes; clotting time, 10 minutes; clot retraction, normal; tourniquet test, positive.

January 8, 1953: Follow-up. One prolonged episode of excessive vaginal bleeding since last visit, ceased spontaneously.

Summary and Conclusions

1. The bleeding manifestations and laboratory data in 199 reported patients with "pseudohemophilia" are reviewed.

2. This diathesis differs from other hemorrhagic states and especially does not fit into the classification of the "hemophilia-like" disorders.

3. Pseudohemophilia occurs in both sexes and is often familial. The authors' cases include Caucasian and Negro patients.

4. The principal clinical manifestations are repeated episodes of abnormal bleeding. The only consistently abnormal laboratory finding is a prolonged bleeding time. The bleeding tendency and the bleeding time in a given patient are variable and unpredictable. Although bleeding episodes are common, the outlook for life is relatively good.

5. The mechanism of the defect in hemostasis is uncertain and may not be the same in all cases. The cases may not all represent a single entity. There is some evidence for both a platelet defect and a vascular defect.

6. There is no satisfactory specific therapy. Since any surgical procedure is a major hazard to these patients, all but the most urgent surgery should be avoided.

Summario in Interlingua

Pseudohemophilia se distingue per le anormalitate laboratorial de un prolongate tempore de sanguination. Le test del consumption de prothrombina es anormal in certe patientes e normal in alteres. Tempore coagulatori, conto plachettal, e tempore prothrombinic es normal. Le retraction del coagulo es usualmente normal, e le test a tourniquet es positive in circa 50 pro cento del patientes.

Es presentate un revista del characteristicas clinic notate in le 13 patientes del autores e le 186 patientes in previe reportos. Iste disordine occurre in ambe sexos e se manifesta usualmente durante le juventute. Sanguination spontanee—excepte ab naso e gingivas—es incommun, sed traumas minor resulta frequentemente in sanguination excessive. Tal sanguination excessive se observa etiam frequentemente durante le menstruation e post parto. Le prognose vital es relativemente bon, sed extractiones dental e interventiones chirurgic es major hazardos. Il existe apparentemente in omne patiente individual un grande variabilitate del tendentia sanguinatori ab un tempore al altere.

Le natura del defecto hemostatic es incerte. Illo non es necessarimente le mesme in omne casos. Il existe indicios de tanto un defecto plachettal como etiam un anormalitate vascular in iste patientes. Casos diagnosticate como pseudohemophilia non representa necessarimente un identic entitate clinic.

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SPLENIC INFARCTION IN SICKLEMIA DURING AIRPLANE FLIGHT: PATHOGENESIS, HEMOGLOBIN ANALYSIS AND CLINICAL FEATURES OF SIX CASES*†

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Evidence has accumulated that individuals with sicklemia, when exposed to decreased oxygen tension during airplane flight, may develop infarction of the spleen. In 1950 Sullivan [1] described one case of sickle cell trait with sudden splenic enlargement following an airplane flight. Since that time several reports from military establishments have appeared in the literature which have confirmed the association of splenic infarction, sicklemia and airplane flight. Cooley, Peterson, Engel and Jernigan [2] reported six cases of massive splenic infarction in Negroes following air travel. Each individual was treated with splenectomy. Two more cases of splenic infarction in Negroes precipitated by aerial flight were presented by Conn.[3] Conservative treatment in both instances was followed by prompt recovery. Doenges, Smith, Wise and Breitenbucher [4] discussed two cases in which sickle cell-hemoglobin C disease was proved by electrophoretic studies in two Negro soldiers who developed splenic infarction after airplane flight. One of their patients was subjected to splenectomy; the other responded to conservative measures. Still another case of splenic infarction associated with aerial flight in a Negro male with a positive sickle cell test was reported by Harvey.[5] Splenectomy was performed in this patient and multiple infarctions were demonstrated.

Smith and Conley [6] recently performed hemoglobin electrophoresis on hemolysates from 15 cases with splenic infarction following air flight. Their series included eight previously reported patients.[2, 3, 4] There were 11 cases with the sickle cell trait, three with sickle cell-hemoglobin C disease, and one probable instance of sickle cell-thalassemia disease (microdrepanocytosis).

During the last year six examples of the clinical triad of splenic infarction, sicklemia and air flight were reported to one of us (A. G. M.)

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from military installations for hemoglobin analysis. Electrophoretic and alkali denaturation technics [7] permitted the distinction of several varieties of sicklemia. It was possible to diagnose sicklemia variants such as sickle cell-hemoglobin C and sickle cell-thalassemia disease. By these methods the sickle cell trait was demonstrated in three patients, sickle cell-hemoglobin C disease in two, and sickle cell-thalassemia disease in one. Only one of the cases was treated with splenectomy. Another was subjected to laparotomy, but the spleen was not removed. The four remaining patients responded to symptomatic measures.

These observations point out that this problem has become of importance in aviation medicine. The pathogenesis of flight-induced splenic infarction is discussed in relation to the amount of sickling hemoglobin in the various types of sicklemia, and the unusual features of the splenic circulation which facilitate sickling are emphasized. Recommendations are made to define the suitability of sicklemia patients for air flight.

Case Reports

Sickle Cell Trait

Case 1. This 21 year old Negro male was admitted to the Francis E. Warren Air Force Base Hospital, Wyoming, on July 11, 1954, after having been removed from an unpressurized airplane en route from Seattle, Washington, to the East Coast. The patient's complaint was pain in the left upper quadrant, which had begun two hours after he left Seattle. This pain had become progressively worse and was associated with both nausea and vomiting. It began initially in the epigastric region, and later localized in the left upper quadrant. The pain was intermittent and cramping and did not radiate.

Physical examination revealed the patient to be in moderate distress. Auscultation of the abdomen disclosed occasional high-pitched tinkles, followed by periods of complete silence. The abdomen was tympanitic and soft but diffusely tender. There was mild rigidity in the left upper quadrant. The patient had scars in the pretibial areas, but he stated that these were the result of injury.

The initial white blood cell count was 10,900/mm.^{3}, with 84% neutrophils. Total red blood cell count was 5.1 million/mm.^{3} and the hemoglobin was 17.0 gm./100 ml. Repeated tests for sickling were done locally and all were reported as negative. However, paper electrophoretic studies demonstrated the sickle cell trait pattern,* and the sickle cell test was positive later (table 1). The serum bilirubin level was normal. Flat x-ray of the abdomen showed ileus of the large bowel in the left upper quadrant. There was no free air under the diaphragm.

Forty hours after admission of the patient to the hospital a surgical exploration of the abdomen was performed because of rising pulse rate and increasing abdominal pain, distention and rigidity. Approximately 100 ml. of free fluid were found in the left upper quadrant near the "slightly enlarged" spleen. Splenectomy was performed. A blood transfusion was given the day after operation.

Pathologic examination of the spleen revealed a massive clot on its antero-inferior surface but no gross infarction. Histologic sections disclosed marked engorgement of the splenic pulp with sickled erythrocytes (figure 1). Splenic culture showed no growth.

* The hemoglobins were separated by paper electrophoresis and quantitated, as previously reported.[7] An "Elphor" densitometer was used.

Comment: The failure to demonstrate sickling of the red blood cells probably resulted from improper technic, since the sickle cell test later was positive and electrophoretic studies exhibited the sickle cell trait pattern. Although actual splenic infarction was not demonstrated, the marked engorgement of the splenic pulp and the evidence of hemorrhage presumably resulted in the left upper quadrant pain and tenderness, and were related to intravascular sickling at low oxygen tension. It is also possible that splenic infarction may have been present under the area of hemorrhage and that histologic sections were not made at this site.

Case 2. A 26 year old Puerto Rican Master-Sergeant was admitted to the U. S. Army Hospital, Fort Lawton, Washington, on October 12, 1954, with the chief complaint of severe left upper quadrant and left flank pain of seven hours' duration. He stated that on the preceding day he had flown by a nonscheduled commercial airline from Puerto Rico to Omaha, Nebraska, with no adverse effects. However, about 30 minutes after the plane left Omaha for Seattle, Washington, he developed a sharp pain in his left flank that radiated under his left costal margin. The pain was intermittent but quite severe, and was aggravated by deep breathing. On one occasion the pain spread to his left shoulder, but it was unassociated with nausea or vomiting. The exact altitude of the flight was unknown. The patient recalled that he had had a similar episode of severe left upper quadrant pain early in 1954 when he flew from California to New Jersey. After he had been in the air for less than one hour the pain became so severe that the pilot thought it best to land at an unscheduled stop in Utah. There the patient was hospitalized for one day before he was permitted to make the trip from Utah to New Jersey by train.

TABLE 1

Hemoglobin Analyses

Case No.	Percentage of Hemoglobin				Interpretation
	A*	S*	C*	F*	
1	56	44	0		Sickle cell trait
2	56.2	43	0	0.8	Sickle cell trait
3	57.5	42	0	0.5	Sickle cell trait
4	0	46.1	53	0.9	Sickle cell-hemoglobin C disease
5	0	53	47		Sickle cell-hemoglobin C disease
6	20.6	76	0	3.4	Sickle cell-thalassemia disease
Normal	98.3 to 100	0	0	0.1 to 1.7	Normal

* A: normal adult hemoglobin. S: sickling (S) hemoglobin. C: type C hemoglobin. F: fetal type hemoglobin.

The patient had been born and reared in Puerto Rico. He was unaware of any Negro blood in his relatives, and stated that his parents and grandparents had been born in Puerto Rico.

On physical examination shortly after admission the patient was found to be an acutely ill man with dark brown skin and matted, curly black hair. His temperature was normal. There was definite splinting on the left side of the chest, with decreased excursion. The left leaf of the diaphragm was elevated about 3 cm. above the right and moved very little with breathing. There was some rigidity but no rebound tenderness in the left upper quadrant. The spleen was not palpable, but there was percussion tenderness over it. No splenic friction rub was heard.

Laboratory studies revealed the following: hemoglobin, 14.0 gm./100 ml.; white blood cell count, 18,650/mm.^{3}, with 88% neutrophils. Urinalysis showed a trace of protein and an occasional white blood cell. On the following day the leukocyte count rose to 19,350/mm.^{3}, but the urinalysis showed no change. The reticulocyte count was 1.8%. Platelets were adequate in number on the blood smear, and the erythrocytes were of normal size and shape. No target cells were seen. Sickling of the red blood cells was demonstrated by the rapid slide technic and by the sealed coverslip method. Paper electrophoretic studies and alkali denaturation revealed the sickle cell trait pattern (table 1). Serum bilirubin was 0.32 mg./100 ml. An x-ray of the chest on admission showed an elevation of the left diaphragm.

The patient's clinical course was characterized by a temperature elevation to 101° F. on the first day. There was a gradual fall to normal by the third day. The patient continued to complain of left upper quadrant pain for about 48 hours after admission. The pain then gradually subsided and the tenderness disappeared completely.

The patient was given Gantrisin and penicillin to prevent abscess formation at the site of infarction. He was discharged from the hospital 13 days after admission, at which time he was completely asymptomatic.

Comment: Although splenectomy was not performed in this individual, the occurrence of splenic infarction following air travel seems highly probable in view of two unrelated episodes of severe left upper quadrant pain that developed on aerial flight in unpressurized planes. The presence of the sickle cell trait in this Puerto Rican soldier presumably was derived from Negro ancestors. This was suggested by the negroid appearance of the patient.*

Case 3. This 22 year old Negro male was admitted to the U. S. Army Hospital, Fort Carson, Colorado, on October 28, 1954, with a complaint of pain in the left upper quadrant. The patient had been in good health until three days prior to admission. On that day he boarded a DC-3 plane which was unpressurized and departed from the West Coast eastbound. After about four to five hours of flight the patient noted dull, steady left upper quadrant pain and a throbbing headache, chilliness and stiffness of the neck. Shortly thereafter he became nauseated but did not vomit. After 45 minutes all complaints disappeared except for the nausea and left upper quadrant pain, which increased in severity throughout the flight. The patient denied any history of anemia and knew of no relatives with such difficulty. He had no history of leg ulcers or pains in the legs or abdomen.

Physical examination on admission revealed the temperature to be 99.4° F. He appeared acutely ill. The abdomen was moderately distended, and bowel sounds were hypoactive. There were extreme tenderness, mild rigidity and some rebound tenderness in the left upper quadrant. Percussion revealed dullness in the left hypochondrium, but no definite mass could be palpated. There was no evidence of scarring of the pretibial areas.

Laboratory studies on admission revealed a leukocyte count of 11,600/mm.^{3}, with a slight left shift of the neutrophils. The hemoglobin was 14.2 gm./100 ml., and the sedimentation rate was 38 mm./hour. The white blood cell count two days later was 24,200/mm.^{3}, with 83% neutrophils. The reticulocyte count ranged between 4.0 to 5.8% on repeated tests, and the hematocrit was 44%. The total bilirubin

* A study of the incidence of the sickling trait in Puerto Rico would be desirable for genetic, anthropologic and practical reasons. There is evidence that the sickle cell trait occurs in significant numbers among the population of other islands in the West Indies.[8]

was 0.88 mg./100 ml. A sickle cell preparation revealed almost complete sickling after 24 hours. Filter-paper electrophoresis and alkali denaturation tests showed the sickle cell trait pattern (table 1). There was no evidence of spherocytosis on the blood smear, and a saline fragility test without incubation was normal. Culture of abdominal fluid obtained by paracentesis showed no growth. A smear of this fluid revealed 80% polymorphonuclear leukocytes. These findings were thought to be consistent with acute peritonitis.

The day following admission the patient was afebrile and much improved, but rigidity in the left upper quadrant remained. An abdominal exploration was performed and the spleen appeared two times enlarged. There was a small raised area on the anterior portion of the spleen which was thought to be an infarct. A splenectomy was not performed. The patient made a complete and uneventful recovery.

Comment: The elevated reticulocyte count of 5.0% cannot be explained by the sickling trait. Although histologic examination was not performed, there seems little doubt that the nodular area in the spleen was an infarct.

Sickle Cell-Hemoglobin C Disease

Case 4. This 18 year old Negro soldier entered Madigan Army Hospital because of abdominal pain of three days' duration. In April, 1954, he had had a bout of cramping abdominal pain lasting for about a day. A month later he began to have periumbilical cramping pain which was relieved by some medicine he received at the dispensary. Although he did not feel well he boarded a westbound transcontinental plane that evening, and an hour after the take-off became nauseated and began to vomit. He vomited intermittently until a few hours after landing the next morning. The day following the flight he noticed a constant left upper quadrant pain on awakening. Moving, being jarred, palpation and even eating aggravated the pain. He had never experienced such pain previous to this episode.

Physical examination on admission revealed a patient in moderate distress and pale in appearance. There was no icterus. Tenderness was present in the left upper quadrant, and visible and palpable fullness was noted in this area. There was increased dullness to percussion in the splenic area. After the abdominal tenderness had subsided the spleen was found to be palpable three fingerbreadths below the left costal margin.

On entry his hematocrit was 37% and the sedimentation rate was 10 mm./hour. The icterus index was 9.0 units. Further blood studies revealed an erythrocyte count of 4.0 million/mm.^{3}, a hemoglobin of 12.3 gm./100 ml., and a reticulocyte count of 3.0%. The leukocyte count was 10,150/mm.^{3} A blood smear showed moderate anisocytosis with numerous target cells. There was slight poikilocytosis. Sickling preparations revealed up to 95% sickling in 24 hours. Electrophoretic analysis and alkali denaturation studies of this patient's hemoglobin demonstrated the pattern of sickle cell-hemoglobin C disease (table 1).

The patient was re-admitted to the hospital three weeks after discharge because of recurrence of left upper quadrant pain with nausea and vomiting. The pain was aggravated by deep breathing. Pain had started the day prior to entry and was improved within 24 hours.

Comment: In a patient with a positive sickle cell test who has splenomegaly and many target cells in the blood smear, a diagnosis of sickle cell-hemoglobin C disease is warranted.[9] This diagnosis was confirmed by electrophoresis. This patient had vague abdominal complaints of a type frequently encountered in sickle cell disease. The flight presumably precipi-

tated splenic infarction. It is of interest that the patient had a recurrent attack of left upper quadrant pain three weeks after the flight.

Case 5. This 20 year old Negro was admitted to Madigan Army Hospital on March 31, 1954, with a history of epigastric pain. Three days previously, approximately 45 minutes after departing from Omaha, Nebraska, on a flight to Seattle, Washington, the patient was awakened by intense left epigastric pain. The pain was constant and radiated to his back. He obtained maximal relief when he assumed a knee-chest position. The patient noted that at the time his pain started the airplane had encountered a storm and was ascending to a higher altitude. He had no knowledge as to whether the plane was pressurized, or at what altitude it was flying. There was no nausea or vomiting. His abdomen felt distended. At the time of his admission to the hospital the epigastric pain was mild and was not at all distressing. He stated that he had never previously experienced any form of abdominal pain, nor had he had any ulcerations of the legs or pain in the extremities.

Physical examination revealed tenderness in the left upper quadrant. The abdomen was muscular and difficult to examine. The spleen was not palpated.

Laboratory examination revealed a white blood cell count of 8,650/mm.^{3}, sedimentation rate of 2 mm./hour, hematocrit of 45%, and bilirubin direct 0.19 mg./100 ml., indirect 1.5 mg./100 ml. Later the leukocyte count rose to 11,750/mm.^{3}, with a differential showing 70% neutrophils and 30% lymphocytes. The reticulocyte count was 3.9%. The red blood cells showed slight anisocytosis, a few polychromatophilic cells and numerous target cells. Platelets were numerous on the blood smear. A sickle cell test was positive. Electrophoretic study of the patient's hemoglobin revealed sickle cell-hemoglobin C disease (table 1).

The abdominal pain on admission was of a mild degree and disappeared over a period of four days. No further therapy was administered.

Comment: This patient had compensated sickle cell-hemoglobin C disease without apparent splenomegaly, although the abdominal rigidity may have made it difficult to palpate an enlarged spleen. Otherwise this case represents a typical example of splenic infarction on air travel.

Sickle Cell-Thalassemia Disease

Case 6. This 19 year old Negro soldier entered the Madigan Army Hospital because of cramping abdominal pain of one day's duration. He arrived in Seattle by plane July 3, 1954, after a 10 hour transcontinental flight during which he was airsick and vomited twice. He felt all right for about an hour after landing but then developed severe, cramping pain. He complained of chilliness and was found to have a temperature of 99.8° F. He was admitted to the hospital on the Surgical Service with a diagnosis of acute appendicitis. The pain then changed and became predominantly left-sided. In the hospital there was tenderness in the upper left abdomen, with moderate rigidity. His temperature initially ranged from 99° to 100° F., but returned to normal five days after admission to the hospital. The patient had had some pain behind his knees previously but no other rheumatic symptoms.

Physical examination revealed mild tenderness over the left lower rib cage on punch and palpation. The spleen was palpable 2 cm. below the costal margin. No icterus was noted.

Laboratory work on entry revealed a white blood cell count of 11,000/mm.^{3}, hematocrit of 40%, red blood cell count of 4.1 million/mm.^{3}, hemoglobin of 12.6 gm./100 ml., and a sedimentation rate of 6.0 mm./hour. The icterus index was 9.0 units. Blood smear revealed a few target cells, hypochromia, poikilocytosis and anisocytosis.

Sickle cell preparation showed 85 to 90% sickle cells in 24 hours. Hemoglobin analysis by electrophoresis and alkali denaturation tests exhibited the pattern of sickle cell-thalassemia disease (table 1).

The initial fever and generalized abdominal pain disappeared, but mild left-sided abdominal and left flank pain persisted for a few days. At the time of dismissal from the hospital he was entirely free from pain.

Comment: Hemoglobin analysis revealed a pattern consistent with sickle cell-thalassemia disease. A major electrophoretic component of sickling (S) hemoglobin (76%), together with a minor component of normal (A) hemoglobin (20.6%) and the elevated fetal (F) hemoglobin (3.4%) (table 1), has been seen only in this disease.[10, 11] The peripheral blood smear showing hypochromia, target cells and variability in size and shape of the red blood cells further substantiated this diagnosis.

Discussion

The reason for the recent increased incidence of splenic infarction associated with aerial flight in individuals with sicklemia is not obvious. The more frequent use of air travel for the transportation of military personnel may be responsible in part, although this mode of travel has been used quite extensively in military service for some time. Certainly, a higher index of suspicion must have played an important rôle in the frequency of diagnosis of this condition during the last year. There is no reason to suspect that the incidence of sicklemia among military personnel has changed significantly.

Pathogenesis

The pathogenesis of splenic infarction in sicklemia poses a number of problems related to the sickling phenomenon and splenic circulation. Intravascular sickling in peripheral venous blood occurs only in patients with classic sickle cell anemia and not in carriers of the sickling trait.[12] Only special devices producing anoxia and increased acidity will induce in vitro sickling in trait erythrocytes.[13] It has been shown that the oxygen tension in vitro has to be reduced to a partial pressure of at least 10 to 15 mm. of mercury before appreciable sickling of trait cells occurs. In contrast, erythrocytes from patients with sickle cell anemia demonstrate the sickling phenomenon at oxygen pressures of 45 to 60 mm. of mercury.[14, 15]

The increased facility with which red blood cells from patients with sickle cell anemia assume the sickled shape under conditions of hypoxia can be readily explained by the larger amount of sickling (S) hemoglobin in such cells. The amount of the abnormal hemoglobin in sickle cell anemia erythrocytes usually accounts for more than 80%—and frequently more than 90%—of the total hemoglobin.[16] Sickling trait cells contain only 20 to 50% sickling (S) hemoglobin.[17, 18] Since only one third of sickling trait patients have more than 40% sickling (S) hemoglobin,[17] the chance of encountering three consecutive unrelated sickle cell trait individuals with

more than 40% sickling (S) hemoglobin is remote.* The remaining three patients had variants of sicklemia, such as sickle cell-hemoglobin C disease [9, 19] (two cases), and sickle cell-thalassemia disease [11] (one case). The amount of sickling (S) hemoglobin in these variants of sicklemia is intermediate (50–80%) [7] between that of the sickle cell trait and that seen in sickle cell anemia (table 1). As expected, in vitro sickling in such cases can be induced by oxygen pressures intermediate (40 mm.) between those required for the sickling of trait erythrocytes and those required for sickle cell anemia cells.[15]

The sickle trait is about 100 times as common as sickle cell-hemoglobin C disease, while sickle cell-thalassemia disease is a still rarer disorder.[20] The fact that seven of the 21 electrophoretically examined cases with this syndrome represented the rare variants of sicklemia is highly significant, and again emphasizes the importance of the amount of sickling hemoglobin in the pathogenesis of flight-induced splenic infarction (table 2).

TABLE 2

Sicklemia Types in 21 Electrophoretically Examined Patients with Flight-Induced Splenic Infarction *

Diagnosis	Number of Cases	Per cent of Total
Sickle cell trait	14	66.7%
Sickle cell-hemoglobin C disease	5	23.8%
Sickle cell-thalassemia disease†	2	9.5

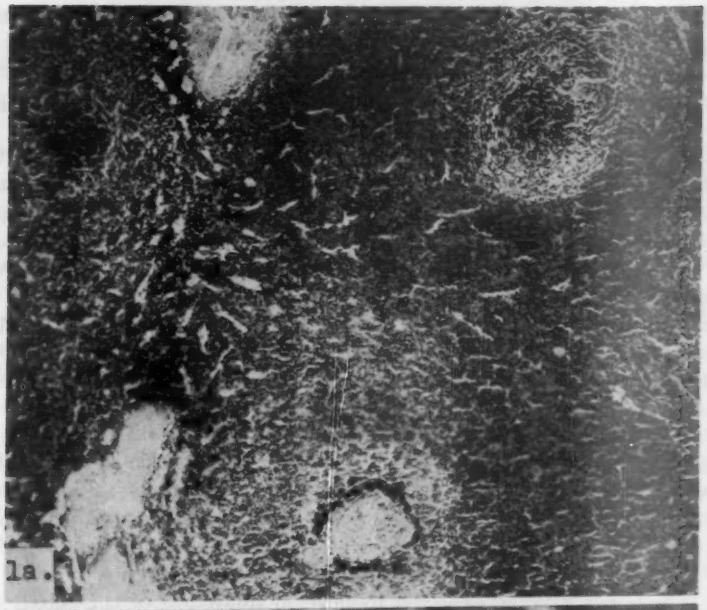
* Cases collected from the literature, including the six herewith reported.

† Case 4 of Smith and Conley[6] (identical with case 5 of Cooley et al.[3]) undoubtedly has sickle cell-thalassemia disease: (a) hypochromic indices; (b) more sickle than normal hemoglobin on electrophoresis; (c) splenomegaly of 460 gm.; (d) 20% target cells in blood smear of the patient and his mother.

No direct data are available on oxygen tension in visceral capillaries. From arterial and venous oxygen tension data, the capillary oxygen pressure may be extrapolated, but it is subject to considerable variation with changes in blood flow. Assuming normal blood flow, an altitude of about 15,000 to 25,000 feet must be reached before the capillary oxygen tension (10 to 15 mm. of mercury) necessary to induce sickling in trait cells is obtained.[21, 22] Thus, when three individuals with the sickling trait were flown to an altitude of 15,000 feet for 10 to 15 minutes, some intravascular sickling in peripheral venous blood was observed.[23]

The special nature of the splenic circulation may permit considerable slowing of blood flow and hemoconcentration in the splenic pulp.[24] Splenic puncture smears from patients with sickle cell anemia showed three to 10 times more sickled cells than the peripheral blood films.[25] Weisman and his co-workers [26] demonstrated an increased concentration of sickle cell

* The probability of finding three such sickling trait carriers of different families is $(1/3)^3 = 1/27 = 3.7\%$.



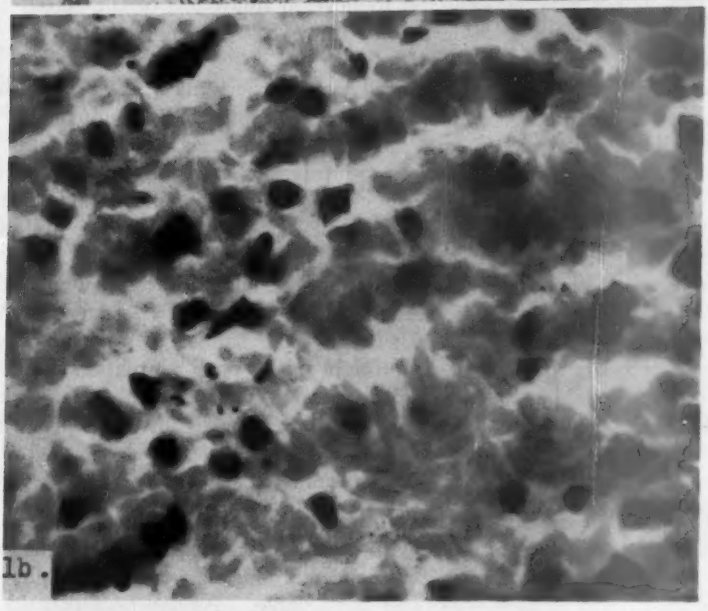


FIG. 1*a*. Low power view of spleen of case 1 (sickle cell trait), showing marked congestion of splenic pulp with erythrocytes.

FIG. 1*b*. High power view (× 1,500) of same spleen. Note masses of sickled erythrocytes in pulp.

anemia erythrocytes in the splenic pulp by direct methods. Sickle cell trait erythrocytes did not exhibit this phenomenon in these experiments. However, hypoxia may bring about sequestration of sickle trait cells, as illustrated by figure 1b, which shows remarkable packing of the splenic pulp with the sickled erythrocytes of case 1 in this study.

Once sickling within splenic capillaries is established there is further slowing of blood flow, with increasing local hypoxia and acidity. As more sickling takes place, viscosity increases [27] until finally infarction ensues. Since the major branches of the splenic artery do not anastomose to any extent, collateral circulation is poor. As a result the spleen is more readily predisposed to infarction.[24]

Splenic infarction at ground level, often accompanied by left upper quadrant pain, characteristically occurs in children and young adults with sickle cell anemia and splenomegaly.[28] Because of these frequent infarctions gradual shrinkage of the spleen occurs until a very small organ is found in adults. Patients with the sickling disease variants (sickle cell-hemoglobin C disease, sickle-thalassemia disease) have insufficient sickle cell hemoglobin to produce multiple infarctions at ground level and their spleens remain enlarged throughout adult life. However, sufficient abnormal hemoglobin is present to cause splenic infarction at relatively low altitudes (4,000 to 6,000 feet), such as those of many commercial airline flights.[6] Sickle cell trait individuals may be expected to develop infarction of the spleen only when flying at high altitude (10,000 to 15,000 feet) in unpressurized planes.

Sickling hemoglobin in sickle cell trait carriers may give rise to other clinical manifestations. The occurrence of idiopathic hematuria in the sickle cell trait has recently attracted attention.[29] Its pathogenesis is not quite clear but presumably is related to intravascular sickling in renal vessels. One of us (A. G. M.) recently observed a patient with the sickle cell trait who had idiopathic hematuria. This developed several weeks following an aerial flight in a pressurized plane. It is conceivable that the flight was instrumental in precipitating the hematuria. Sudden deaths due to sickling in cerebral vessels have also been reported in patients who may have had only the sickling trait.[30] These patients have had severe central nervous system depression due to anoxia brought on by poor ventilation. Electrophoretic hemoglobin studies of postmortem blood specimens from cases of sudden death among Negroes should be carried out to solve this problem.

Prevention

From these considerations certain recommendations can be made. Thus, carriers of the sickle cell trait with 20 to 35% sickling (S) hemoglobin may be in less danger of developing splenic infarction on aerial flight than those with 35 to 50% sickling (S) hemoglobin. As had been pointed out, all of our patients fell into the group with the higher amount of sickling (S)

hemoglobin. Preferably, sickle cell trait carriers should not fly in unpressurized planes at high altitudes. If high-altitude flying becomes necessary in these planes, oxygen equipment should be provided to such individuals. Patients with sickle cell-hemoglobin C disease or sickle cell-thalassemia disease, and patients in the splenomegalic phase of sickle cell anemia should not fly at all unless ground level pressure can be maintained. Even mild hypoxia corresponding to an altitude of 4,000 to 6,000 feet, such as is encountered in pressurized planes, might precipitate splenic infarction in these individuals.[6] These conclusions make it advisable that Negroes and Puerto Ricans who fly frequently be screened for the various manifestations of sicklemia.

The ordinary sickle cell tests are nonspecific for the differentiation of sicklemia subtypes and may be misleading in unskilled hands. Many false-negative tests [6] and occasionally false-positive results [31] have been recorded. Screening by the technically simple paper electrophoresis in selected centers would be the method of choice [7, 32] and could be used for mass surveys, such as on induction in the Armed Forces. Hemoglobin solutions for testing could be prepared from the blood clots which are now discarded during performance of the routine serologic tests for syphilis. A definite diagnosis of the subtypes of sicklemia could be made by this method.*

Treatment

Cooley et al.[2] were of the opinion that the best treatment for splenic infarction precipitated by air travel is early splenectomy. They removed the spleen in all six of their cases. Splenectomy was deemed necessary in one of the two cases treated by Doenges et al.[4] whereas the other responded to conservative management. Vascular embarrassment of the bowel was suspected in the case observed by Harvey [5] and a laparotomy was performed. The surgeon found a greatly enlarged spleen which appeared to be obstructing the colon, and splenectomy was performed. On the other hand, nonsurgical management with symptomatic therapy proved to be entirely satisfactory in the case reported by Sullivan,[1] in the two cases of Conn,[8] in one of the two cases of Doenges,[4] and in four of the cases described in this report. One of the patients in this study was splenectomized, and another had a laparotomy but the spleen was not removed.

It appears that the average case of splenic infarction precipitated by air travel does not require splenectomy but may be treated symptomatically. Careful observation by both internist and surgeon is recommended. Should there be progressive signs of peritoneal irritation, or a protracted febrile course, splenectomy may be advisable. However, the mere presence of fever and leukocytosis is no indication for surgery. If a patient has a

* Inductees with sickle cell anemia, sickle cell-hemoglobin C disease and sickle cell-thalassemia disease should be rejected for military service. In all these rare conditions hemolytic disease is present, and these patients might have difficulty if subjected to the rigors of military life. Individuals with the sickle cell trait are, of course, acceptable for military service.

markedly enlarged spleen, such as in sickle cell-hemoglobin C disease, splenectomy may also be indicated in view of the danger of rupture. Splenectomy, however, will not affect the patient's basic disease process.

Summary

1. Splenic infarction precipitated by airplane flight was observed in five Negroes and one Puerto Rican soldier with sicklemia.

2. Hemoglobin analysis revealed three patients with sickle cell trait, two with sickle cell-hemoglobin C disease, and one with sickle cell-thalassemia disease (microdrepanocytosis).

3. It is suggested that the following factors play a rôle in precipitating this syndrome: (a) hypoxia; (b) amount of sickling (S) hemoglobin (more than 40% in all six cases); (c) peculiarities of the splenic circulation: slowing of blood flow in the pulp, and poor collateral blood supply between splenic arterial branches.

4. The following criteria for air travel of persons with sicklemia are suggested: (a) Individuals with sickle cell trait should not fly at high altitudes in unpressurized airplanes unless a source of oxygen is available. (b) Individuals with splenomegalic sickle cell anemia, sickle cell-thalassemia disease and sickle cell-hemoglobin C disease should not fly unless ground level air pressure can be maintained.

5. Nonsurgical symptomatic treatment of flight-induced splenic infarction appears sufficient for most cases. However, splenectomy may be required in selected instances.

6. The occurrence of splenic infarction in individuals with the sickle cell trait emphasizes that this common condition can no longer be considered entirely benign.

7. It is desirable that the Armed Forces institute a paper electrophoretic screening program for the detection of sicklemia among Negro and Puerto Rican military personnel on induction. Similar screening tests should be performed on any Negroes who fly repeatedly.

Summario in Interlingua

Patientes con drepanocytemia pote disveloppar infarcimento splenic durante viages aeree. Un soldato portorican e cinque soldatos negre con iste syndrome esseva studiate. Analyses hemoglobinic per medio de electrophorese a papiro e tests de denaturation de alcali revelava tres casos de character drepanocytic, duo casos de drepanocytemia plus morbo a hemoglobina C, e un caso de drepanocyto-thalassemia (microdrepanocytemia).

Le aspectos clinic esseva crampos abdominal e dolor (o dolor sub pression) in le quadrante sinistro-superior durante e post le viage aeree. Le condition duceva in omne casos al hospitalisation del patiente, sed splenectomia esseva executate in solmente un caso. Le presentia de hemoglobina drepanocytic esseva le characteristica de omne nostre patientes e de omne le altere casos reportate in le litteratura.

Nos opina que le sequente factores es significative in le precipitation de iste syndrome: (1) Hypoxia. (2) Quantitate del hemoglobina drepanocytic. (In nostre

casos illo amontava a plus que 40 pro cento.) (3) Peculiaritates del circulation splenic, le quales permitte un relentamento del fluxo sanguinee in le pulpa e provide un inadequate apporto collateral de sanguine inter le splenic brancas arterial.

Nos propone le sequente criterios pro aeroviages de personas con drepanocytemia: (a) Personas con le character drepanocytic non deberea volar a alte altitudes in non-pressurate aeroplanos, a minus que un fonte de oxygeno es disponibile. (b) Individuos con anemia drepanocytic, con drepanocytemia plus morbo a hemoglobina C, o con drepanocyto-thalassemia non deberea volar si le provision de aeropression de nivello terrestre non es possibile.

Le occurrentia de infarcimento splenic in individuos con le character drepanocytic sublinea le facto que il es non plus possibile considerar iste condition commun como integremente benigne.

Il es desirabile que le Fortias Armate institue un programma de secernage a electrophorese a papiro pro deteger al momento del recrutamento le presentia de drepanocytemia in negros e portoricanos. Simile tests deberea esser executate pro omne negros qui vola repetitemente.

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THE BECK OPERATIONS FOR CORONARY HEART DISEASE: AN EVALUATION OF 63 PATIENTS SELECTED FOR OPERATION *†

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THIS is a report of 63 patients who were selected for one or the other of the Beck operations for coronary heart disease at University Hospitals of Cleveland. A committee of three physicians selected the patients for operation, and examined and observed them preoperatively, during the operation, during convalescence, and in each of the follow-up periods. All of the patients were operated upon by Dr. Claude S. Beck under uniform conditions.

The surgical methods of increasing coronary artery flow fall into two categories:

1. Those aimed at increasing vascular communications between the myocardium and extracardiac structures: (a) by the pericarditis produced by abrasion,[1, 2] or by pericardial irritants (such as talcum or asbestos);[3] (b) by fusion of the surface of the myocardium with the omentum,[4] or with pectoral muscles;[2] (c) by implanting arterial blood vessels directly into the myocardium.

2. Those seeking to increase intercoronary communications and blood flow (a) by ligation of the coronary sinus,[6, 7, 8] (b) by arterialization of the coronary sinus.[9, 10]

We shall now define the operations performed in this study.

The Beck I operation "consists of abrasion of the epicardium and lining of parietal pericardium, application of an inflammatory agent (0.2 gm. of powdered asbestos) to these surfaces, partial occlusion of the coronary sinus where it enters the right auricle and grafting of parietal pericardium and mediastinal fat to the surface of the heart."[10] Data concerning the efficacy of these procedures have been reported by Beck and others.[11, 12, 13, 14] Pericardial abrasion and adhesions are induced to produce intercoronary vessels and to provide extra coronary collaterals in an effort to cause a flow of arterial blood from high pressure in the extracardiac tissues to the low

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pressure in the coronary arterial bed. Burchell,[15] in experimental studies on the dog, concluded that the rôle played by vascular channels in pericardial adhesions in supplying blood to the myocardium is minimal or nonexistent. Burchell also emphasized the presence in dogs' hearts of a large septal branch artery, the free anastomosis between the ventricular and the auricular coronary branches, and the extracardiac communications with the great vessels at the base of the heart of the dog. The partial coronary sinus ligation increases interarterial coronary anastomoses by the resultant mild anoxia of the myocardium, as shown by Eckstein.[16]

The Beck II operation, the operation of arterialization of the coronary sinus, consists of two stages and occasionally three. In the first stage a vein graft is placed between the aorta and the coronary sinus, providing a direct communication between these vessels. Stage two is the narrowing of the coronary sinus to 2 to 3 mm. two or three weeks later. This latter procedure provides an escape channel for the arterialized blood, which passes from the aorta to the coronary sinus if the pressure in the coronary sinus becomes excessive. This safety valve prevents over-engorgement of the myocardium. Stage three (performed in five patients) consists of complete ligation of the coronary sinus at a later date. In his original description of the operation Beck anastomosed an artery to the coronary sinus and ligated the coronary sinus in one stage. Because of the incidence of myocardial infarction and of venous engorgement of the myocardium, the one-step operation was discontinued.

Experimental Evidence of Protective Value of the Beck II Operation

Extensive experimental work by Beck[9] showed that arterialization of the coronary sinus, in both the acute and the chronic dog, will protect the myocardium against major coronary artery ligation. Back-flow studies indicate that blood gives up oxygen as it passes reversely through the capillary bed. Retrograde flow from the distal end of a major coronary artery in a normal dog is almost 3.4 c.c. per minute. After the Beck II operation this flow increases to 7.5 c.c. after the first step, and up to 20 c.c. after the second stage. This blood is venous, indicating that the blood from the graft has presumably passed through the myocardial capillary bed and that oxygen has been extracted. After several months the retrograde flow becomes red and arterial collateral circulation is abundant. The operation produces functionally significant intercoronary arterial communications, which persist for at least one year in the presence of an open graft, and for at least three months after the ligation of the graft. The increase in back-flow in the experimental animal prevents ventricular fibrillation and death following coronary ligation. Extensive experimental studies have been made by Eckstein on dogs operated upon by the Beck II technic.[16]

Clinical Study of Patients Selected

Of the 63 patients chosen as suitable for operation, many had intractable angina refractory to medical therapy. Some were accepted for operation who had had previous infarction but were asymptomatic. The operation was done for prophylactic purposes. Patients were rejected who were over 60 years of age (with one exception, a patient aged 66), or who had hypertension of over 160 mm. of Hg, large hearts, signs of congestive failure or active peptic ulcer. There were 60 males and three females. Their ages ranged from 31 to 66 years, and the majority were between 40 and 60. Moderate hypertension was present in three, inactive peptic ulcer in 11, cholelithiasis in six, diabetes in five, and induced hypothyroidism in three. There were two drug addicts. Efforts were made to exclude patients who gave a history of infarction in the six month period immediately preoperative.

Preoperative Myocardial Infarction

Fifty-two patients (82.5%) had infarction preoperatively by either electrocardiogram or visualization at operation, or by examination at autopsy. Six patients (cases 13, 17, 19, 53, 60 and 61) had had electrocardiograms prior to admission which showed evidence of myocardial infarction, whereas the electrocardiograms after admission failed to show any evidence of infarction. Of these, the diagnosis of infarction was verified at operation in three instances (cases 53, 60 and 61) and at autopsy in two (cases 13 and 17). In six others the electrocardiogram failed to show evidence of infarction at any time, but an infarct was found in all either at operation or at autopsy. Of these, five were posterior (cases 1, 6, 9, 34 and 46), and one (case 35) had multiple areas of fibrosis in the left ventricle. In three (cases 22, 27 and 50) old posterior infarction was diagnosed preoperatively, but at autopsy an undiagnosed recent posterior infarction was found in addition to the old ones. In two (cases 54 and 60) an old anterior infarction was diagnosed preoperatively, but at autopsy additional recent posterior was found in one and an old posterior in the other. In one patient (case 12) an old posterior infarct was diagnosed preoperatively but at autopsy both posterior and anterior infarctions were found. In one patient (case 56) both anterior and posterior infarctions were noted at operation, although the electrocardiogram had failed to show evidence of either.

Preparation of Patients

Most of the patients presented themselves with the hope that the operation would relieve pain and prolong life. They believed that the procedure would provide a positive approach to the relief of coronary insufficiency. All patients remained ambulatory until the day of operation. They were maintained on a balanced diet and given sedation as indicated. Digitalis

was not given preoperatively early in the study, but many were digitalized after the first or second stage because of cardiac failure. Dr. Beck ordered preoperative digitalization in the last half of the cases, because of the observation that digitalized dogs withstand cardiac surgery well. Instability of the blood pressure during induction of anesthesia was more frequent in the nondigitalized than in the digitalized group, and supraventricular tachycardia was more frequent in the former. In two of the digitalized patients (cases 45 and 54) Cedilanid was given intravenously at operation, with rapid cessation of the supraventricular tachycardia. A detailed study of the effect of preoperative digitalization will be reported in a later paper.

Anesthesia was induced by intravenous sodium pentothal, followed by nitrous oxide. Ether-helium mixture was used for maintenance of anesthesia. The Rand-Wolfe positive pressure respiration was used with intratracheal intubation in all patients.

Operative Course

During operation there was close coöperation between surgeon, anesthetist and a medical cardiologist. The heart was constantly monitored by the Cambridge Cathode Ray Oscilloscope. In the noncardiac part of the operation changes occurred similar to those noted in thoracotomies: fluctuations in blood pressure and downward displacement of the pacemaker. Dissection or traction of the coronary sinus and in the region of the A-V node produced ST-T changes of ischemia and disturbances in cardiac mechanism. After the aorta-coronary sinus shunt was opened, a temporary drop of systolic and diastolic pressures occurred in 70% of the cases. Epicardial abrasion produced ventricular premature beats in all cases. The development of delayed intraventricular conduction was serious, since nine of the 11 patients showing this conduction defect died during operation.

Selection of Operations

The Beck I operation was done in eight patients in whom for various reasons, technical or otherwise, it was impossible to place the vein graft.

The Beck II procedure was chosen as the more suitable operation in 55 of the present series. Forty-nine of these had a direct aorta-coronary sinus anastomosis or a venous graft communication.

Six patients who were selected for the Beck II operation could not have the aorta sinus graft placed. The reasons for this failure are shown in the following table:

Case No.	Reason for Not Placing the Graft
12	Heart stopped when pericardium opened
27	Supraventricular tachycardia; ventricular fibrillation
32	Supraventricular tachycardia; died 2 hours later
4	Died while vein graft was in process of removal
30	Shock during anesthesia; recovery; no operation
35	Died on table

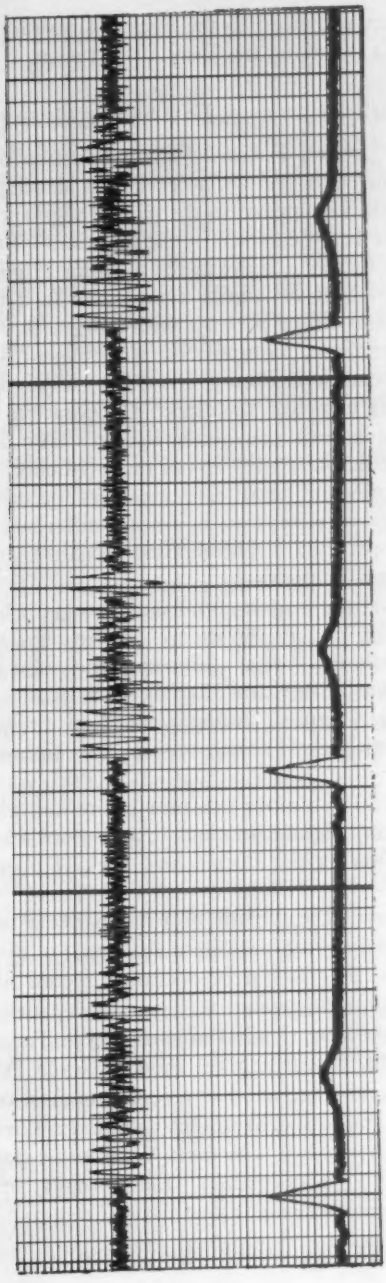

FIG. 1. Murmur of aorta-coronary sinus shunt, recorded in the back, over the spine of the scapula.

Five patients were subjected to the Beck III operation because of heart failure or tachycardia following the Beck II operation.

Clinical Findings Following Operation

Murmur of A-V Shunt: Following the production of the venous shunt a continuous murmur with systolic accentuation developed. The murmur was heard in the back, just medial to the middle segment of the spine of the left scapula, and was best heard during inspiration. Patency of the graft was judged clinically by the presence of the murmur (figure 1).

Changes in Heart Size Following Operation: In a review of the comparable roentgenograms of 10 patients with no grafts or with thrombosed grafts, there was significant postoperative enlargement of the heart in only two, while in 23 patients with open grafts there was significant enlargement in 11. Two patients who had the Beck III operation had smaller hearts after the coronary sinus was completely ligated. We are indebted to Dr. F. A. Rose for reëvaluation of the films of these patients.

Pulse Rate: Significant heart rate increases occurred following both types of operation, but there was no significant difference in the tachycardia of the two types of operation. Thrombosed or patent grafts likewise made no difference in the group appraisal.

Blood Pressure: There was no significant change in blood pressure after the Beck II operation, and no difference between the patients with open and those with thrombosed grafts. Likewise, the pulse pressure after both types of operations was not greatly altered, with occasional exceptions.

Circulation Times: Arm-to-tongue circulation times before and after operation (Beck I and Beck II) with open and thrombosed grafts were not significantly altered.

Venous Pressure: The venous pressure before and after the two operations did not reveal any significant change, and there was no difference between the results following the Beck I and Beck II operations (with open and closed grafts).

Ballistocardiograms: The records of a few patients taken preoperatively and postoperatively showed no consistent changes.

One patient (case 54) had a preoperative record alone (Grade III), as he died on the eighth postoperative day. One patient (case 41) had a preoperative record showing Grade I abnormality. Ten days after the first stage procedure the ballistocardiogram showed Grade IV abnormality, and 20 days after the second stage another record was even more bizarre. The day after the second stage, and again six days later, the ballistocardiogram showed Grade IV abnormality. In case 40 the preoperative ballistocardiogram showed Grade II abnormality. Eleven days after the first stage operation the fairly marked respiratory variation disappeared and the ballistocardiogram was normal. Nineteen months later (18.5 months after

the second stage) the ballistocardiogram was again normal. In one patient (case 19) there was no preoperative ballistocardiogram, but a record 13 months after the second stage was normal. A second ballistocardiogram 18 months later (31 months after the second stage) showed Grade III abnormality. The final ballistocardiogram, four months after the Beck III operation, was normal. We are grateful to Dr. Irving Liebow for the interpretations of the records.

Master Tests: The single standard Master Test was done in 57 patients before operation. These tests were regarded as positive in 37 (64.9%). In 28 patients the test was repeated after complete recovery. Four tests which were positive before surgery became negative (one with the Beck I, two with the Beck II with thrombosed grafts, and one with the Beck II and an open graft). On the other hand, there were five whose negative tests became positive, all with the Beck II operation. Four of these had open grafts and one had a thrombosed graft.

In 68% of the postoperative records there was no change in the test over its preoperative status.

Additional Physiologic Tests

Cardiac Output: In patients having the Beck II operation with thrombosed grafts there was no significant change in cardiac output. With open grafts, varying degrees of increased cardiac output and blood volume indicated that an increased cardiac load had been imposed by the fistula. The inability of the heart to withstand the stress of the fistula in some instances appears to be related more to the individual cardiac reserve than to volume of the shunt (calculated from data obtained by cardiac catheterization). Details of these studies will be published separately.

Clinical Appraisal

Clinical appraisal of the results of the operations after recovery and in the follow-up period was recorded by a scale:

E: Excellent. Disappearance of all pain, and return to gainful employment.

G: Good. Almost complete relief of pain; very little nitroglycerin requirement; able to return to work.

U: Unimproved.

UE: Unable to evaluate.

The patients were evaluated at six month intervals.

Evaluation: Thirty-six patients who had various types of operations and who lived six months or longer after operation were appraised by the committee. The data are shown in table 1.

Nineteen (52.8%) of all 36 patients who lived longer than six months

were classed as excellent or good. Postoperative evaluations were made at from six months to five years, the majority in the one to three year period.

In the six patients who had the Beck I operation and who lived six months or longer (one to five and one-half years, and for an average period of 26 months), two are classed excellent, three are unimproved, and one cannot be evaluated because of postoperative schizophrenia.

Of the 22 patients with patent grafts at the second-stage operation who could be evaluated, 14 fell into the class excellent or good (74%). One patient (case 13) died three years after the Beck II and immediately following the Beck III. Of the eight patients with thrombosed grafts who could be evaluated, three were excellent or good (43%).

Of the five patients who had the Beck III operation, the results in four are regarded as excellent. One patient died in the first postoperative day.

Figure 2 is a summary of all 63 patients selected for one of the operations. Eight patients had the Beck I operation, and 49 patients had either the first

TABLE 1

Evaluation of Patients Living Six Months or More

Type of Operation	No. Cases	Excellent or Good	Unimproved	Unable to Evaluate	Died Later
Beck I	6	2	3	1	0
Beck II					
Graft open	22	14	5	3	3
Graft closed	8	3	4	1	0
Beck III*	5	4	0	—	1

* These five cases are included in the 22 patients who had the Beck II operation and who had patent grafts.

stage of the Beck II or the complete operation. The operation was done in one stage (direct aorta-coronary sinus fistula) in four patients, the graft alone was placed in 12, and in 28 the two-stage operation was done. The graft remained patent in 19 and became thrombosed in nine. The graft could not be placed in six. In five patients the Beck III operation was done following the Beck II because of either congestive failure or tachycardia.

Operative Mortality: In the eight patients in our series who had the Beck I technic there were no operative deaths. (In 17 patients who had the Beck I operation at Lakeside Hospital from September 1, 1953, to May 1, 1954, *after* completion of the present study, there were *three deaths.*)

Of the first 13 patients with the Beck II procedure there were nine operative deaths, whereas of the last 50 patients (with 43 Beck II operations) there were 13 deaths (26%). One patient died on the second day after the Beck II operation. There were, in addition, five other deaths well after operative recovery.

The causes of operative deaths included myocardial hemorrhage, shock, congestive failure, acute myocardial infarction, infarction of spinal cord,

hemorrhage in the posterior wall of the chest and abdomen, probably due to anticoagulant therapy, ventricular fibrillation, pulmonary infarction and aspiration atelectasis. Fresh or healing myocardial infarction was found post mortem in four instances. The age was judged by the pathologist as older than the postoperative period. The history and the electrocardiogram gave no clue as to this recent infarction. In four cases the estimated age of the infarct led to the conclusion that infarction was related to the operative procedure, perhaps the result of the hypotensive state during or after operation or altered dynamics of the coronary circulation. In all of these cases the Beck II operation had been done. Case 1 had the Beck II in one stage,

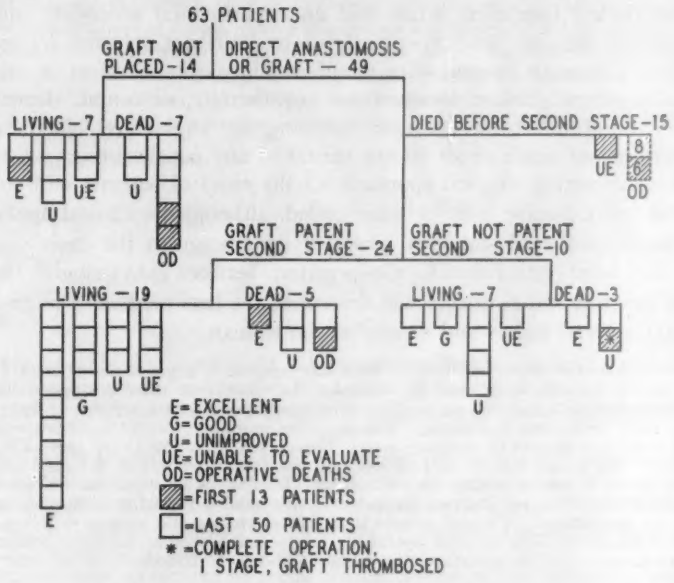

FIG. 2. Summary of all patients selected for operation.

and in one patient the Beck III procedure had also been performed (complete ligation of coronary sinus).

CONCLUSIONS

The Beck I operation—mechanically induced pericarditis and partial coronary sinus ligation—has a sound experimental background. The number of patients subjected to this procedure was small, and the final appraisal must await further evaluation. In our series of eight cases there were no operative deaths. From data derived from Lakeside and Mt. Sinai Hospitals Dr. Beck estimates the mortality at 5% or less.

The Beck II operation also has a valid experimental background and is effective in enabling the dog to withstand coronary artery ligation. "The application of data on dogs with normal coronary arteries to human beings with occlusive coronary disease requires reserve and caution."[6] In man, the operation is difficult to perform and lengthy.* The operative mortality was approximately 25%. The operation, in addition to its production of intercoronary vessels, actually adds a burden to the heart and circulation by increasing cardiac output and blood volume. In a few instances there was increase in blood pressure and in heart rate. In some patients cardiac failure was induced and the coronary sinus had to be ligated. This operation, then, in its present state of development, should be held in abeyance.

The Beck I operation, while still an experimental procedure, may be reserved for patients who are invalided by pain not relieved by medical therapy. Coronary disease, when manifested by angina of effort or emotion, is usually severe. Improvement from any therapy, of course, depends on the remaining intact musculature receiving an augmented blood supply. The data in our small series do not permit of any conclusions.

This interesting surgical approach for the relief of patients with arteriosclerotic heart disease is to be commended, although its clinical application must be limited until statistical proof of its efficacy in the cases operated upon has been established.† Coöperation between physiologist, experimental surgeon and physician will determine the best method of augmenting coronary arterial supply and its application to man.

Note: Since this paper was written Beck has reported a larger series of Beck I operations. In 103 patients who could be evaluated six months or more postoperatively 45% had no pain and 45% had less pain; 35% were better able to work without limitations and in 55% there were some limitations. The operative mortality was 6.6%. (Scientific basis for the surgical treatment of coronary artery disease, J.A.M.A. **159** (13): 1264–1271, 1955.) Beck says "We expect life to be prolonged by operation, and this is the most important purpose of our extensive studies on this subject. It is desirable to measure this aspect of the work by operating on alternate patients and determining mortality in both groups, but this is for the future." We still believe that control studies and long-term follow-up are necessary before the Beck or other operations become established as definitive treatment for coronary disease. In the meantime this operation should be considered as an experimental procedure.

SUMMARIO IN INTERLINGUA

Isto es un reporto de 63 patientes seligite como appropriate al un o al altere del operationes Beck. Omne le operationes esseva executate per Dr. C. S. Beck.

Le operation Beck I consiste de abrasion de epicardio e pericardio parietal, application de un agente inflammatori (asbesto), occlusion partial del sinus coronari, e graffage de pericardio parietal e grassia mediastinal al superficie del corde.

Le operation Beck II produce arterialisation del sinus coronari in duo o tres stadios. In le prime stadio un graffo venose es placiate inter le aorta e le sinus coronari. Le secunde stadio occurre duo o tres septimanas plus tarde e effectua le

* The patients who survived the Beck II operation and who were observed six months or longer had a high percentage of good and excellent results (65%). The patients who had open grafts had excellent or good results in 74%.

† A further study of the natural history of patients with arteriosclerotic heart disease must be made to provide control data.

restriction del sinus coronari a 2 a 3 mm. Le tertie stadio (executate in cinque patientes) consiste del complete ligation del sinus coronari a un periodo plus tarde si disfallimento cardiac ha supervenite.

Le patientes seligite pro le operationes habeva in lor majoritate un intractabile angina que esseva refractori al therapia medical. Alicun patientes esseva seligite pro rationes prophylactic. Illes habeva habite infarcimento cardiac e esseva asymptomatic.

Selection del Operation: Le operation Beck I esseva executate in octo patientes in qui le placiamento del graffo venose esseva impossibile pro rationes technic o altere. In 55 patientes le operation Beck II esseva seligite como plus appropriate. In sex de iste casos le execution del operation seligite non esseva possibile.

Studios Physiologic: In patientes subjicite al operation Beck II con graffos thrombotisate il habeva nulle significative alteration del rendimento cardiac. In casos con graffos aperte, varie grados de augmento in rendimento cardiac e volumine sanguinee indicava que le fistula habeva causate un augmento del carga cardiac.

Evalutation: Le resultatos esseva classificate como "excellente" (E = disparition de dolor e retorno al empleo), "bon" (B= quasi complete alleviamento de angina e possibilitate de retornar al empleo), "non-meliorate" (NM), e "non-evalutabile" (NE) a causa de previe absentia de symptomas o del stato emotional.

Tabula de Evalutation:

	Total	E o B	NM	NE	Moriva Plus Tarde
Beck I	6	2	3	1	0
Beck II					
Graffo Aperte	22	14	5	3	3
Graffo Claudite	8	3	4	1	0
Beck III	5	4	0	—	1

Dece-nove (52, 8 pro cento) del 36 patientes con Beck I o Beck II e superviventias de plus que sex menses esseva E o B. Le evalutationes post-operative esseva facite post inter sex menses e cinque annos, in le majoritate del casos post inter un e tres annos.

Mortalitate Operative: Inter le octo patientes con Beck I il habeva nulle morte. In 17 patientes in qui le operation Beck I esseva executate post le completion del presente studio il habeva tres mortes operative. Inter le prime 13 patientes subjicite al operation il habeva 9 mortes; inter le ultime 50 patientes (includente 43 operationes Beck II), il habeva 13 mortes (26 pro cento).

Ben que ambe operationes ha solide bases experimental, lor application a humanos con morbo coronari debe esser manipulate cautissimemente. Evalutationes futur va revelar le valor de iste operationes, con plen consideration del grande variation del superviventia probabile in patientes con morbo de arteria coronari.

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EVALUATION OF AORTIC OCCLUSION BY AORTOGRAPHY *

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AORTOGRAPHY, or the contrast visualization of the aorta and its branches, has played an important part in recent advances in diagnosis. Although abdominal aortography is not new, only within the past decade has it been established as more than a medical adventure. Following the report of Smith [1] and his associates of over 1,000 uncomplicated aortic punctures for renal arteriography, there has been a widespread acceptance of aortography in this country. Apparently the reasonable safety of this procedure without any important complications in their report was sufficient to overcome the understandable hesitancy of physicians to puncture the aorta. Also, the development of improved contrast dyes has lessened the skepticism relative to this procedure.

The technic which we have been using is essentially adopted from that of Smith, Rush and Evans.[2] Breakfast is withheld, and preoperative doses of atropine and morphine are given one hour prior to the scheduled puncture. A test for sensitivity to the contrast media is made sometime prior to the aortic injection. Anesthesia is induced with Sodium Pentothal, and the patient is intubated and turned prone on the x-ray cassette. A scout film is taken to check position, bowel shadows and suitable exposure with the roentgen unit. Ordinary intravenous, infusion-type polyethylene tubing approximately 50 cm. long, with adaptors at each end, is attached to the syringe, and 30 to 40 c.c. of the contrast media solution are drawn up. A 6 inch, 18 gauge needle is introduced below the left twelfth rib, 6 to 8 cm. lateral to the spinous process of the corresponding vertebra. It is directed cephalad, medially and anteriorly to strike the body of the eleventh or twelfth vertebra. This depends upon the level at which one wishes to visualize. To visualize the renal vessels the needle should strike the body of the eleventh thoracic vertebra. The needle is slightly withdrawn, directed more medially and advanced. This is repeated until the needle point slides off the antero-lateral aspect of the vertebral body. The stylet is removed and the needle advanced through the aortic wall. At this point a sense of decreased resistance is felt and blood flows freely from the needle. The tubing is secured to the needle. Blood is aspirated into the syringe to assure that there are no air bubbles in the tubing. We use a home-made wooden syringe stand

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to hold the syringe stable and vertical. Sufficient force is exerted on the syringe barrel to assure delivery of the dye within three to four seconds. The x-ray is taken during injection of the last 5 c.c. of the dye. Timing is extremely important, as the dye is propelled quickly by the aortic blood flow. We have been routinely using an eight film rapid cassette changer in our recent aortograms. However, this is not necessary to visualize the aorta, because the exposure in the first second is the one which most clearly demonstrates the aorta. This is equivalent to a single film exposure. When an attempt is made to visualize the renal parenchymal vessels, however, a rapid cassette changer is extremely valuable, as it most certainly exposes a film in the third and fourth seconds. This appears to be the ideal time for demonstration of maximal filling of these vessels.

Arteriosclerosis is a generalized disease but is spotty in distribution. Arteriosclerotic changes occur throughout the aorta but may progress more rapidly in certain specific localities. These severe localized lesions not uncommonly result in total occlusion due to loss of elasticity, deposition of fatty material, ulceration and fibrosis and, finally, thrombosis.[3] The significance of segmental obstruction of major arteries has surgical implications, due to the availability of surgical technics for the removal of such localized obstructions.

The patient with a high arterial segmental block generally has the symptom of intermittent claudication, without rest pain and trophic skin changes. Examination shows an absent or a greatly diminished oscillometric excursion and absent pulsations in the femoral arteries, without the marked changes of ischemia in the feet. This circumstance is due to the development of adequate collateral circulation allowing for adequate blood flow to the distal parts to maintain adequate skin nutrition.

Aortic Aneurysm

Kampmeier [4] observed 65 cases of abdominal aneurysms, the majority of whom had had symptoms for less than one year. In his series death occurred within one month of hospitalization in 30 patients. Colt [3a] found the average duration of life in instances of abdominal aneurysm to be only one year after the appearance of symptoms. According to Estes,[5] the survival rate for patients with abdominal aneurysms who were asymptomatic at the time of diagnosis was no better than for those patients who had symptoms. The survival rate was much lower than that of the normal population of age 65. All patients died within 10 years of diagnosis. It is recognized that the prognosis for individuals with abdominal aortic aneurysms is shorter than for individuals of a similar age group without abdominal aortic aneurysms. It is all the more serious when such individuals with abdominal aneurysms have symptoms. The warning signal is the onset of symptoms attributable to the aneurysm, usually pain in the abdomen or back, with or without radiation into the lower extremities. Figure 1 is an aortogram of

a 65 year old man with abdominal pain. The dilatation and tortuosity of the abdominal aorta are evident.

Chronic Aorto-iliac Occlusion

Leriche [6] described a syndrome characterized by fatigability of the lower extremities, intermittent claudication, genital impotence, ischemic pallor, global atrophy of the lower extremities, without trophic lesions of the distal parts of the skin, absence of major pulses, and absent oscillometric excur-

Fig. 1. Dilatation and tortuosity of the low abdominal aorta. Note the clearly outlined kidney parenchyma.

FIG. 2. Leriche syndrome, illustrating complete obstruction of low abdominal aorta with good collateral circulation. Note the lipiodol residual at L-5. This man had been operated upon for a herniated disc two years previously.

sions. Figure 2 shows one of our cases following this pattern quite closely from the clinical evaluation and confirmed by aortography. This diagnosis can be made by clinical means in most instances. However, like others,[7] we believe that it cannot be distinguished from bilateral obstruction of the common iliac arteries, which produces a very similar picture.

The general opinion is that chronic aorto-iliac obstruction is not a primary obstruction in the aorta because the arterial lesion is rarely localized in the terminal aorta. The process generally begins in one or both iliac

arteries and extends cephalad until the aorta is completely thrombosed in its distal portion. The thrombus may extend upward to involve vital major arterial branches, causing death. Figure 3 illustrates bilateral renal artery involvement in a 42 year old white man with severe hypertension and papilledema. The aortogram outlines the left hypoplastic kidney and decrease in size of left renal artery and stenosis of the right renal artery at its exit from the aorta. This case represents a Goldblatt kidney in the original meaning, as both renal arteries are partially occluded, and the prognosis is grave.

FIG. 3. Goldblatt kidney. Complete obstruction of terminal aorta involving stenosis of both renal arteries, with a hypoplastic kidney on the left. The inferior mesenteric artery is visualized.

SEGMENTAL THROMBOSIS AND STENOSIS OF MAJOR ARTERIES

Anatomic obliteration of segments of major arterial channels is frequent, according to Julian et al.[8] Factors such as flexion of the knee, compression of the superficial femoral artery by the adductor magnus, and trauma at the aortic bifurcation may aggravate an already existing degenerative process, finally culminating in an obstructing thrombosis. The patient with a segmental arterial occlusion has intermittent claudication. The signs of distal ischemia, such as coldness, marked dependent rubor and ulceration, may be absent. This is in contrast to the ischemic changes seen when the occlusive

process diffusely involves the major vessels distally in the lower extremities. In both instances there may be a loss of pulses high in the involved extremity. Confirmation of the diagnosis of a segmental arterial block with demonstration of reëntry of collateral blood flow distal to the obstruction rests upon the arteriogram.

Figure 4 illustrates these observations in a 70 year old white man with a stenosis of the right common femoral artery. This man could walk only one to two city blocks without claudication. Femoral pulsations were absent. Wylie and McGuinness [9] classify 12 patients in whom a segmental zone of arteriosclerotic narrowing was the sole demonstrable cause for the presenting

FIG. 4. The arrow points to a stenosis of the right common femoral. There is adequate blood flow distal to the stenosis.

complaints of arterial insufficiency. They conclude that arteriostenosis of sufficient degree to produce ischemic symptoms represents an almost complete arterial occlusion and is a frequent intermediary stage in the development of arteriothrombosis.

The method suggests probabilities of usefulness in the diagnoses of splenic artery aneurysms, calcifications in the abdomen, and in cysts and neoplasms of the pancreas not identifiable by conventional studies. Currently we have been investigating the diagnostic usefulness of arterial visualization by

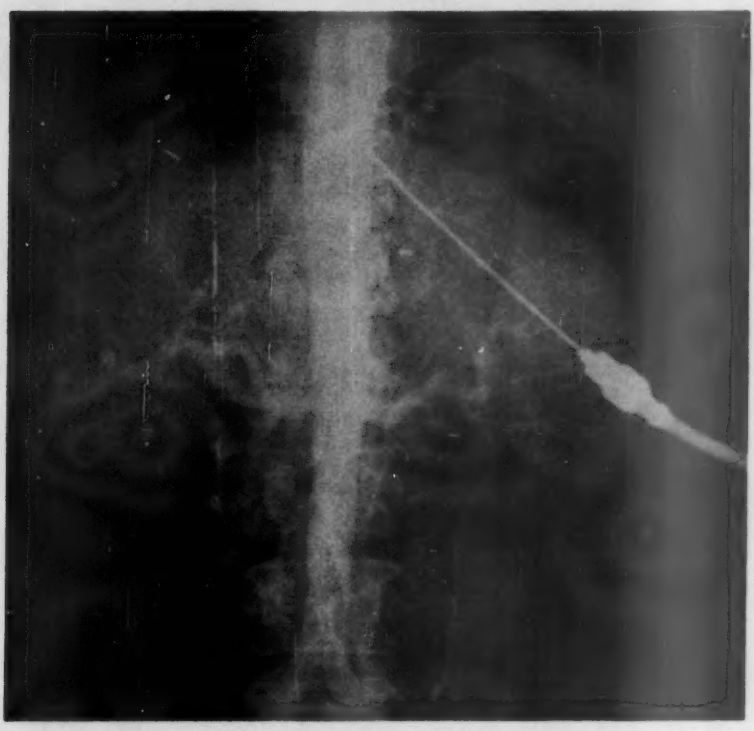

FIG. 5. Nephrogram illustrating rotation and flattening of inferior pole of the left kidney. A palpable mass was present. The surgical specimen was a retroperitoneal fibrosarcoma intimately involving the renal capsule.

aortography in various abdominal and retroperitoneal tumors (figure 5). We hope to present these studies in a subsequent report. Milanes et al.[10] have already indicated certain indirect evidences of tumors of the liver by means of aortography.

SUMMARY

The technic of visualization of the aorta and its major ramifications in the diagnosis of disease of major vessels and organs has been discussed briefly.

Aortograms are illustrated which allow us to believe that this is a readily available method for determining the topography of vascular lesions when clinical evidence suggests their presence.

Aortography has become a necessary diagnostic technic for the precise visualization of the location and extent of segmental obstruction of the aorta and its major branches. Such localization is a prerequisite to definitive surgical treatment.

SUMMARIO IN INTERLINGUA

Aortographia—i.e. le visualisation a contrasto del aorta e su brancas—ha essite un factor importante in recente progressos diagnostic. Manipulate dexteremente, le methodo se ha provate satis secur e libere de importante complicationes. Nos presenta un revista del preparation del patiente e del technica usate in le injectiones. In certe casos il es necessari executar un test del sensibilitate del patiente al substantia de contrasto ante que isto es injicite in le aorta. Atropina e morphina es administrate un hora ante le punction aortic. In le serie hic presentate, le patientes esseva anesthesiate per medio de Pentothal-Natrium. Postea le intubation esseva executate. Il es necessari facer un film exploratori pro verificar position, umbras intestinal, e exposition roentgenographic. Pro assecurar le visualisation del vasculos renal, le agulia debe entrar in le aorta a un puncto opposite al dece-prime vertebra thoracic. Le colorante debe esser expedite a in le aorta intra tres a quatro secundas. Le autores ha laborate con rapide cambiamento de cassetta. In tentar a visualisar le vasculos parenchymal renal, le uso de un rapide cambiator de cassettas es importante proque illo expone un film in le tertie e quarte secundas post le injection del colorante, lo que es apparentemente le tempore ideal pro observar ille vasculos in stato de plenamento maximal.

Arteriosclerose es un morbo generalisate, sed su distribution es sporadic. Alterationes arteriosclerotic occurre ubique in le aorta, sed illos pote progreder plus rapidemente in certe sitos specific. Le signification del obstruction segmental de arterias major es apparente ab le puncto de vista chirurgic, proque nos dispone de technicas chirurgic pro le ablation de obstructiones localisate. Nos differentia le aspecto clinic de occlusion segmental arterial ab le arteriosclerose diffuse que causa le obstruction. Nos describe aneurysma aortic, chronic occlusion aorto-iliac (syndrome de Leriche), thrombosis segmental, e stenosis de arterias major. Pro omne typo nos presenta un aortogramma illustrative.

Nos demonstra le valor del aortographia in le diagnose differential de chronic obstruction aorto-iliac e de obstruction bilatere del commun arterias iliac. Le confirmation del diagnose de bloco arterial segmental con re-accesso del fluxo sanguinee collateral a un puncto ultra le obstruction depende del aortogramma in su differentiation ab plus extense alterationes occlusive organic que presenta un simile aspecto clinic de insufficientia arterial. Il es probabile que le methodo pote provar se utile in le diagnose de aneurysma del arteria splenic, de calcificationes abdominal, e de cystes e neoplasma in le pancreas que non es identificabile per studios conventional. A iste tempore le autores investiga le utilitate diagnostic del visualisation arterial aortographic in casos de varie tumores abdominal e retroperitoneal. Un tal caso es illustrate.

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ON THE CHOICE OF TREATMENT FOR HYPERTHYROIDISM *

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During the last 50 years there have been repeated sweeping changes in the management of hyperthyroidism. The changes have veered from emphasis on radical surgery to conservative surgery, away from surgery altogether and toward medicine, and away from medicine toward radioactive iodine. The emphasis probably will continue to shift until the etiology of hyperthyroidism has been established and the disease can be attacked specifically at its origin or, better still, prevented.

It was in 1869 that Cheadle [1] reported excellent results in the treatment of hyperthyroidism with iodine, but the medical world was unconvinced. For many years recognized authorities warned against the use of iodine and thus robbed surgery of a now-recognized aid. Then, in about 1925, the use of iodine in the treatment of hyperthyroidism suddenly was rediscovered and recognized as lessening somewhat the hazards of surgery. Many more operations were performed and, while many lives were undoubtedly prolonged, there were also many postoperative deaths. Roentgen treatment was tried and produced some good results, and perhaps some skin cancer too. It since has been discarded.

Despite all the changes during the last 30 years, surgery has continued to hold a strong place in the treatment of hyperthyroidism, having been made safer by iodine and almost completely safe by combinations of iodine and antithyroid drugs. Surgery and antithyroid drugs thus retain significant rôles in treatment; nevertheless, their relative importance in recent years has been overshadowed by that of radioactive iodine. For more than 15 years the use of radioactive iodine has continued steadily to gain wider acceptance.

Current Types of Therapy

Our modern armamentarium in the treatment of hyperthyroidism includes: (1) iodine; (2) antithyroid drugs alone, or (3) antithyroid drugs in various combinations with iodine, with roentgen therapy, or with thyroid feeding; (4) surgery, and (5) radioactive iodine (I^{131}).

Iodine: Iodine, one of the oldest forms of treatment, still has several outstanding uses in the management of hyperthyroidism. It is the preferred treatment in thyroid crisis, a condition that was relatively common 25 years ago but today apparently is rare. In this country the iodine usually is given

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as Lugol's solution, in a dose of 1 c.c. three times daily, but often may be given more conveniently as 5 gr. enteric-coated tablets of potassium iodide. If the patient's condition is not critical and radioactive iodine is available, I^{131} may be given first, followed by normal iodine.* Iodine alone is used by many surgeons in the preoperative preparation of patients having mild or moderate hyperthyroidism. In diagnosis it occasionally occurs that after clinical or laboratory studies have been completed there may remain doubt whether hyperthyroidism is present. In such doubtful cases iodine may be given for a three-week therapeutic trial. However, when I^{131} therapy is anticipated, such a therapeutic trial has the disadvantage of blocking thyroid uptake of radioactive iodine for three or more weeks after the trial has ended. The antithyroid drugs, on the other hand, decrease the effectiveness of I^{131} for only a few days after their withdrawal.

It is doubtful that iodine ever is the preferred drug for definitive treatment of hyperthyroidism; even in the mildest cases, antithyroid drugs are preferable unless they are not tolerated.

Antithyroid Drugs: The term "antithyroid drugs" usually means a group of substances each of which has an action like that of thiouracil. These substances block enzyme action that is necessary for the synthesis of thyroid hormone. Under their blocking effect, after the stored as well as the circulating hormone has been dissipated, the patient's state may be transformed from hyperthyroidism into hypothyroidism.

The list of antithyroid drugs includes: methylthiouracil; propylthiouracil; iodothiouracil;† Tapazole‡ (methimazole) (Mercazole in Great Britain), 1-methyl-2-mercaptoimidazole; and Neo-mercazole, which is 2-carbethoxy-thio-1-methylglyoxaline. Each possesses the same advantage in that each is highly effective in the control of hyperthyroidism in an easily administered, low-cost oral dose. Patients do not develop tolerance or fastness to these drugs, and after they are discontinued the patient is left with an intact thyroid gland and almost never with lasting hypothyroidism. The latter is a particular advantage in younger patients, especially children. Each of the antithyroid drugs also has, in some degree, the same inherent weaknesses: (1) toxic effects in some patients; (2) post-treatment recurrence rate higher than that following surgery or I^{131} therapy; (3) enlargement of the thyroid (usually transient) during treatment in some patients; and (4) necessity for dependence on the patient for administration.

The effective dosage of propylthiouracil or methylthiouracil is approximately 200 to 600 mg. per day, whereas that of Tapazole or Neo-mercazole is about 20 to 70 mg. per day. If we take propylthiouracil as an example, it is generally conceded that some toxic effect may be expected in 1 or 2%

* Since thyroid crisis has many features to suggest that it is due to severe hyperthyroidism with superimposed acute adrenal failure, cortisone also should be kept in mind as a possible important adjunct to treatment.

† Itrumil Sodium—Ciba Pharmaceutical Products, Inc.

‡ Eli Lilly and Company.

of the patients treated. Usually only fever or a mild rash will appear, but severe dermatitis has been reported and, rarely, agranulocytosis has occurred. Although agranulocytosis is rare, the possibility of its development is disturbing and the patients must be taught the possibly serious significance of sore throat or fever. Fortunately, the condition usually can be adequately treated with blood transfusions and antibiotics.

As to the choice of antithyroid drug, our preference still is propylthiouracil; we shall continue to use it until convincing evidence shows another drug to be more effective and/or less toxic.

McGavack and his group [2] believe that methimazole is less toxic than propylthiouracil; they found toxic reactions in eight of 189 patients treated with methimazole. Davidson's [3] experience has led him to the opposite conclusion, and other authors [4, 5, 6] have reported the development of agranulocytosis following methimazole therapy.

Each time a new antithyroid drug appears the hope of achieving effectiveness without toxicity is reborn. Neo-mercazole is the newest to appear. Doniach [7] observed no toxic effects of Neo-mercazole among 120 patients, and Fraser [8] reported only one instance of toxicity among 41 patients when he used an initial dose of 30 mg. and a maintenance dose of 15 mg. per day.

A recent development that will bear watching concerns the antithyroid effect of potassium perchlorate. In 1952 Stanbury [9] called attention to the fact that this salt blocks I^{131} uptake and causes a rapid release of previously accumulated iodine from the hyperthyroid gland. Last spring in *The Lancet* Morgans and Trotter [10] announced that there had been no toxic effects in 108 hyperthyroid patients treated with potassium perchlorate. Hyperthyroidism was well controlled in 24 to 25 previously untreated patients; however, control was achieved more slowly than it would have been if methylthiouracil had been used. Control of the hyperthyroidism was maintained by doses of potassium perchlorate in 62 of 64 patients who had been on maintenance doses of methylthiouracil immediately prior to the institution of the perchlorate therapy.

Antithyroid Drugs with Other Forms of Therapy: When surgery is advisable it is common practice to administer *iodine* for one or two weeks preoperatively to patients who have been treated with antithyroid drugs, to produce a decrease in vascularity of the gland; apparently it is effective, since there is rapid disappearance of a bruit if present over the gland. Whether it is good practice to give concurrently or even beneficial to give iodinated thiouracil rather than uniodinated, is not quite so certain. Catz and Starr's [11] data appear to show that in hyperthyroid patients iodothiouracil produces a more rapid effect than thiouracil, while iodine itself is both less effective and less sustained in its effect. The work of Vanderlaan [12] with rats fed iodothiouracil, however, indicates that the effects are only those to be expected from a thiourea compound and not those of iodine.

Antithyroid drugs have been used in conjunction with *roentgen therapy* [13] in an attempt to produce more lasting remissions, but this combination has produced remissions lasting more than six months in only 67.5% of cases, a percentage no greater than that which others have shown to occur without the use of roentgen therapy.

Some workers use *thyroid feeding* concurrently with antithyroid drugs, to provide the use of effective doses of antithyroid drugs without initiating hypothyroidism or encouraging pituitary hyperfunction.[14] We believe this to be a particularly useful maneuver in pregnancy, where hypothyroidism is to be meticulously avoided.

Indications for Use: We believe that antithyroid drugs are particularly useful under the following circumstances:

1. In the preoperative preparation of patients in whom any hyperthyroidism produces added risk.
2. For long-term therapy in Graves's disease, in an attempt to produce lasting remission, especially in a young patient or in one whose goiter is not very large.
3. For long-continued use, possibly with no plan to discontinue it, if surgery or I^{131} treatment is unavailable or surgery unsafe or unacceptable.
4. During pregnancy, especially if used with thyroid feeding during the last half of the gestation period.

Such treatment is less clearly indicated in nodular goiter, because control may be slow and the goiter may remain; or in postoperative recurrences of Graves's disease because, in our experience, lasting remissions are uncommon and I^{131} therapy is particularly efficient.

Results: It is our practice to continue treatment for a year after control has been obtained before attempting to withdraw the drug. The rate of recurrence of hyperthyroidism after cessation of administration of antithyroid drugs varies in numerous reports from 20 to 50%. The best results are to be found in groups of patients selected because they have diffuse goiters that are not postoperative recurrences and not extremely large in size.

In Rose's [15] series of 46 patients who were treated with antithyroid compounds and traced one-half to six years, 82.6% remained in remission. In 60 of our own patients who were treated with propylthiouracil and followed one-half to four years, 77% remained in remission,[16] and in Aspenström's [17] series of 42 patients who also were treated with propylthiouracil, 70% were in remission after a year.

Surgery: Surgery not only has been long established as good treatment for hyperthyroidism, but also it is better today than ever before. Despite other developments, some physicians of great experience continue to prefer surgical treatment in most cases. Today the mortality of thyroid surgery performed by experienced surgeons usually is a small fraction of 1%.

Surgery is most clearly indicated for hyperthyroidism occurring in association with any one of the following conditions: clinically diagnosed solitary adenoma, because it is a true neoplasm; large nodular goiters; goiters producing pressure symptoms; and cardiac disease necessitating rapid control of hyperthyroidism (in a patient who is a good surgical risk).

Surgery is less clearly indicated for Graves's disease, especially of the recurrent type; postoperative morbidity is high because of the frequency of trauma to the parathyroid or recurrent nerves. In many medical centers surgery is considered to be the preferred treatment for all patients with Graves's disease who are less than 35 years of age, and by some it is considered preferable to radioactive iodine in patients even up to 50 years of age. In young patients with Graves's disease I recommend surgery only after a thorough trial of antithyroid drug therapy has failed; in patients more than 35 years of age with Graves's disease I very rarely recommend surgery in preference to I^{131} therapy.

The disadvantages of surgery are evident. They include: (1) recurrence in Graves's disease (approximately 5 to 15%); (2) hypothyroidism (perhaps 10%); (3) parathyroid tetany, or (4) recurrent nerve injuries (approximately 1%); (5) a small but nevertheless present mortality rate (0.25%); (6) discomfort associated with the operation; (7) period of hospitalization, and (8) time lost from work.

Radioactive Iodine: Since its inception, the record of efficiency of radioactive iodine in the treatment of hyperthyroidism with diffuse goiter of Graves's disease type has been consistently and almost miraculously good. Since effective dosage varies greatly, nodular goiter with hyperthyroidism must be carefully segregated diagnostically if the response to treatment in all cases is to be high. In general, I^{131} is not considered the preferred treatment for toxic adenoma in the majority of cases.

The possibility of producing cancer many years after treatment with I^{131} is still to be kept in mind but, fortunately, in thousands of patients so treated that specter has not yet appeared. Sometimes after a diffuse goiter has shrunk to nearly normal size a nodule will be evident. The possibility of carcinoma in such a nodule must be considered, as it is known that diffuse glands occasionally harbor small carcinomas, usually of the papillary type.

There are three theoretic disadvantages. The first is common to other forms of treatment, namely, the disease is not treated at its source; second, an intact thyroid gland does not remain; third is the fear of carcinogenesis, which to the present is not supported by fact. The only real disadvantage is the possible development of hypothyroidism. In our own experience a recent careful survey of 325 cases shows that 9% developed an apparently permanent hypothyroidism following I^{131} therapy. Of five clinicians prescribing radioactive iodine, those prescribing from the most careful calculations and the most conservative dosage levels reported that only 4.4% of their patients developed hypothyroidism; others prescribing more from general clinical criteria reported 14%.

Estimation of Dosage: Our method of estimating the dosage is simple. The size of the thyroid gland is estimated in grams. A 24-hour I^{131} uptake is measured; an initial dose of I^{131} is then prescribed which is calculated to deliver 100 microcuries per gram of thyroid. Clinical judgment is used: if the gland is small, the uptake high and the patient young, the calculated dose is lessened. On the other hand, if the gland is large, the uptake not high, the patient elderly and the urgency for cure great, the calculated dose is increased. After two months a new calculation is made. If the basal metabolic rate is above plus 20%, we usually give more I^{131}, increasing the dose over the original if the basal metabolism has risen, repeating it if there has been little change. If the basal metabolic rate is about plus 20% and improvement still is associated with a high uptake, we are inclined to give more I^{131}. If, however, the uptake is low, we are inclined to wait longer. By this means, hyperthyroidism has been controlled in 75% of patients by the use of a single dose, in 15% by two doses, and in the remaining 10% by more than two and occasionally by as many as six doses.

Indications for Use: Radioactive iodine therapy is most clearly indicated in cases of: (1) postoperative recurrences; (2) Graves's disease in patients more than 40 years of age; (3) old age; (4) poor cardiac status; (5) severe concurrent disease; (6) recurrent hyperthyroidism after antithyroid drugs, and (7) preference of either the patient or the physician.

It is contraindicated in pregnancy, but if given inadvertently will do no harm within the first 14 weeks of gestation because the fetal thyroid has an insignificant uptake before that time.[20]

Some of the outstanding advantages of I^{131} therapy in Graves's disease are:

(1) Mortality is zero. It is possible that a patient with impending crisis may be precipitated into a state of active thyroid crisis because of thyroid-gland breakdown following treatment. The case reported by Freitelberg [18] may be an example of such a sequence. It is possible that in a rare instance inadequate therapy, by postponing control, might permit cardiac decompensation to become fatal. This, however, is much more likely to occur in nodular goiter than in Graves's disease.

(2) There is no cord paralysis.

(3) There is no permanent tetany; one example of post-I^{131} tetany of a temporary type is reported in the literature.[19]

(4) Control is complete in almost 100% of patients.

(5) Thyroid size usually is reduced to nearly normal.

(6) There is no discomfort.

(7) There is no disability from treatment and usually no time lost from work.

(8) Recurrence is almost unknown.

(9) Recurrence, if present, can be safely and effectively treated with additional I^{131}.

Results: In the treatment with I^{131} of 1,235 patients with Graves's disease we have seen only two failures: one patient was close to crisis with continuous vomiting, and treatment was withheld too long; another, after 11 months of therapy (90 mc. of I^{131}) was still hyperthyroid and was submitted to surgery. To my knowledge there have been only eight recurrences. Six of these might better be classed as persistent hyperthyroidism. For example, in the record shown on the accompanying graph (chart 1)

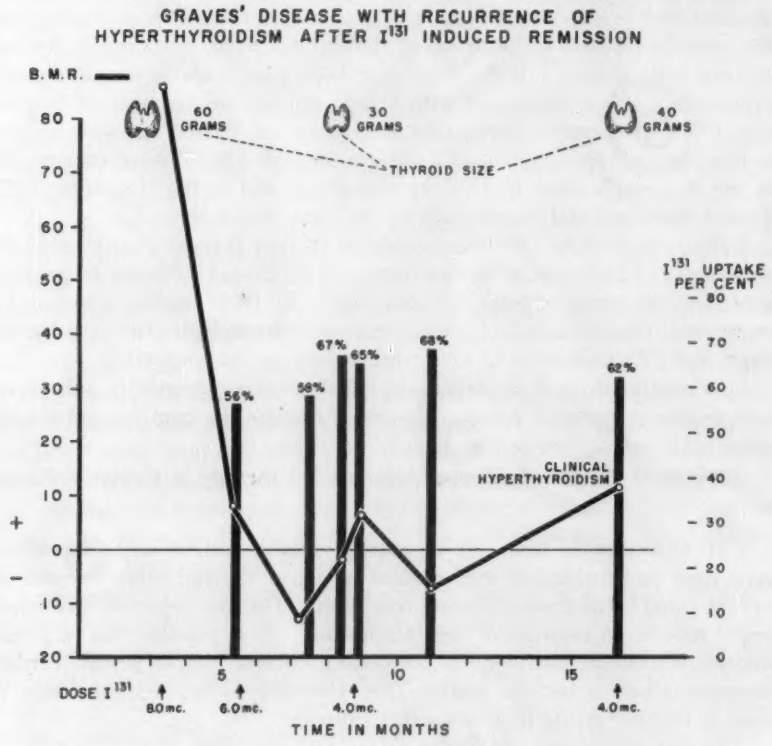

CHART 1.

it will be noted that, although the basal metabolic rate attained normal range, the I^{131} uptake remained throughout in the range commonly seen in hyperthyroidism. Although the last basal metabolic rate shown in the chart is not abnormally high, the patient was judged on clinical grounds to have hyperthyroidism. The fact that recurrence is possible, however, is demonstrated by the courses in two patients having myxedema in whom hyperthyroidism reappeared a year or more after therapy. The course of one of these is outlined in chart 2. The patient had received propyl-

thiouracil for one year, during which time the hypermetabolism had been controlled. When propylthiouracil (P. T. U.) was withdrawn, the hyperthyroidism recurred (noted on chart). At the time the basal metabolic rate that is plotted for 0 months (chart 2) was obtained, the patient again had been receiving propylthiouracil (P. T. U.) but the hyperthyroidism had not been controlled. The propylthiouracil was discontinued at the time of the first basal metabolic rate test shown on the chart. He was clinically euthyroid four months after the second dose of radioactive iodine.

I^{131} can be used to great advantage in nodular goiter with hyperthyroidism if surgery cannot be accomplished safely. Recent experience has shown

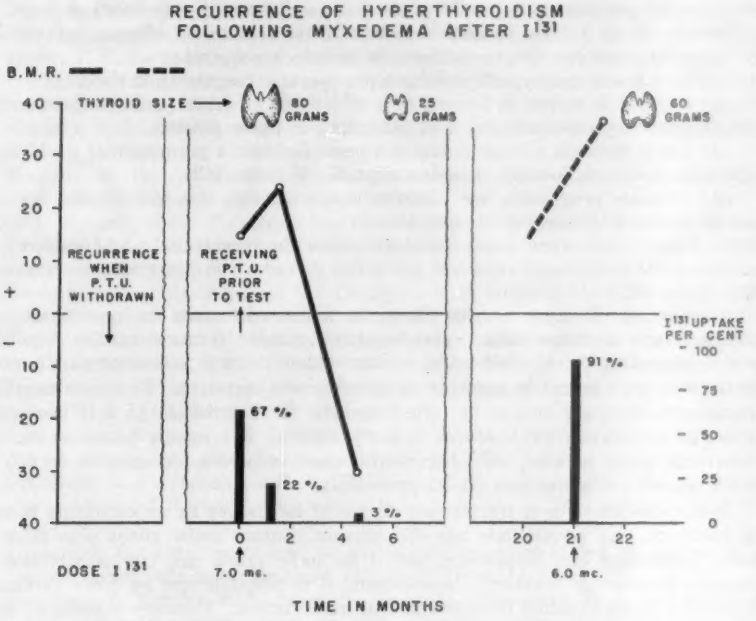

CHART 2.

that an initial dose of 50 mc. produces much more prompt and complete results than does an initial dose under 30 mc. In some cases there is great reduction in the size of nodules, an advantage in the management of intrathoracic goiter.

SUMMARIO IN INTERLINGUA

Nostre armamentario moderne include iodo, drogas antithyroide (sol o in varie combinationes con iodo, roentgenotherapia, alimentation thyroide), chirurgia, e iodo radio-active.

Iodo continua esser le tractamento de election in crises thyroide. Illo es preferite

per multe chirurgos como le sol preparation pre-operative in hyperthyroidismo leve o moderate. Quando le diagnose es dubitose, un therapia probatori de tres septimanas pote esser utile. Iodo es apparentemente nunquam preferite como tractamento definitive.

Drogas antithyroide del typo de thiourea e de typos affin es in uso commun. Illos es efficacissime in dominar hyperthyroidismo. Illos es administrabile per via oral a basse costo. Il non ha disveloppamento de resistentia. Si remission resulta, le glandula thyroide es intacte. Isto es un avantage in feminas e juveniles. Le vitios de iste drogas include (1) effectos toxic, (2) plus alte procentages de recurrentia post-tractamental que post chirurgia o therapia a iodo radio-active, e (3) in certe casos allargamento del struma (usualmente de forma transiente).

Dosages efficace de propylthiouracil o methylthiouracil es 200 a 600 mg per die; de Tapazolo o Neo-mercazolo, 20 a 70 mg per die. Effectos toxic occurre in 1 a 2 pro cento del patientes. Agranulocytosis (un possibilitate disquietante) es rar.

Perchlorato de kalium, secundo demonstrationes recente, ha effectos antithyroide.

Le indicationes pro drogas antithyroide include le sequente:

(1) In casos in que hyperthyroidismo pre-operative augmenta le risco.

(2) In casos de morbo de Graves, in le effortio de producer remission permanente, specialmente in juvene patientes o in patientes con parve strumas.

(3) Como therapia a longe durantia o possibilemente a permanentia, si chirurgia o therapia a iodo radio-active non es acceptabile o disponibile.

(4) Durante pregnantia, specialmente in combination con alimentation thyroide post le medietate del periodo de gestation.

In morbo de Graves (non includente casos de recurrentia post-operative), le procentage de remissiones reportate pro series de casos con parve strumas amonta a 70 e mesmo 82.

Intervention chirurgic es plus clarmente indicate in casos de hyperthyroidismo occurrente con adenoma solitari, grande struma nodular, o morbo cardiac requirente un domination rapide. Le indication de intervention chirurgic es minus clar in morbo de Graves, specialmente in casos de recurrentia post-operative. Le disavantages del tractamento chirurgic include (1) alte frequentia de recurrentias (5 a 15 pro cento) in morbo de Graves, (2) risco de hypothyroidismo, (3) tetania parathyroide, (4) recurrente lesion nervose, (5) disconforto, costo, e perdita de tempore, e (6) un parve sed definite mortalitate (0, 25 pro cento).

Iodo radio-active in le tractamento de morbo de Graves ha un excellente historia de successos. Le possibilitate que illo provoca cancere multe annos plus tarde ha essite mentionate con disquietude, sed il ha nulle prova que iste possibilitate ha unquam devenite un realitate. Nonobstante, il es possibile que on trova carcinoma in nodulos in un glandula tractate con iodo radio-active. Hypothyroidismo es le sol complication post-operatori. Su frequentia varia ab 4 a 15 pro cento. Le dosage es a determinar super le base del dimensiones del glandula e de accordo con le acception del dose traciator. Cento mg per gramma de thyroide es le quantitate de iodo radio-active retenite que produce remission complete in circa 75 pro cento del patientes tractate. Tres quintos del remanente 25 pro cento require duo tractamentos; le resto require tres o plus.

Iodo radio-active es indicatissime in recurrentias post-operatori, in morbo de Graves in patientes de plus que 40 annos de etate, in casos de debilitate cardiac, in le presentia de sever disordines simultanee, in recurrente hyperthyroidismo post therapia a drogas antithyroide, e quando le medico o le patiente lo prefere. Iodo radio-active es contra-indicate in pregnantia, sed si illo es administrate in consequentia de inadequate informationes, illo non es nocive durante le prime 14 septimanas del gestation.

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BACTEREMIA OWING TO GRAM-NEGATIVE BACILLI: EXPERIENCES IN THE TREATMENT OF 137 PATIENTS IN A 15-YEAR PERIOD *

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THE evolution of effective antibiotic therapy has greatly altered the outlook of many infectious states, one of which is the invasion of the blood stream by microörganisms. With the multiplicity of antimicrobial agents now available, it behooves the physician to acquaint himself with the type of therapy most effective in any given infection.

Experience with bacteremia at the Mayo Clinic before and after the advent of sulfonamide compounds was reported previously.[1] More recently, some aspects of bacteremia owing to *Escherichia coli*,[2] *Aerobacter aerogenes*,[3] *Pseudomonas aeruginosa*[4] and proteus organisms[5] were reviewed.

The present study was undertaken to review all cases of bacteremia due to gram-negative bacilli, exclusive of cases of typhoid fever, brucellosis and bacterial endocarditis, seen and treated at this institution during the 15-year period 1940 through 1954. We attempted to include only those patients from whom two or more positive blood cultures were obtained and in whom it was obvious, from clinical examination, that true bacteremia was present. Victims of so-called transient bacteremia, such as one encounters in patients who have just undergone urologic or dental instrumentation and in whom bacterial invasion of the blood stream is fleeting, are not included.

CAUSATIVE ORGANISM

One hundred thirty-seven cases of bacteremia caused by gram-negative bacilli were included in the study. The distribution of these cases according to the organism responsible for the bacteremia is shown in table 1. *E. coli* accounted for approximately half of these infections. *E. coli* and *A. aerogenes*, which may be considered together as the "coli-aerogenes group," were the etiologic agent in 100 of the 137 cases. To consider these two organisms together is probably preferable because of the difficulties encountered in distinguishing them by routine bacteriologic methods. However, for purposes of analysis and in keeping with the practice of other authors, herein we discuss them separately.

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Age and Sex

The ages of the patients varied from six days to 87 years (table 1). Ninety-one were males and 46 were females. The male patients were most heavily concentrated in the age period 40 through 79 years, for 72 of the 91 were in this age group. The female patients, however, were most heavily

Table 1

Distribution of Patients According to Age, Sex and Causative Organism in 137 Cases of Bacteremia Due to Gram-negative Bacilli

Organism	Sex	Age, years									Total
		0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	
Escherichia coli	M	2		2		4	11	14	11	3	76
	F	2		1	6	5	3	8	3	1	
Aerobacter aerogenes	M	2			1	2	3	6	4		24
	F					1	1	1	2	1	
Proteus	M			1	2	1		2	3		14
	F				1		1	1	1	1	
Pseudomonas aeruginosa	M	1			1		4	1		1	12
	F	1			1	2					
Bacteroides	M			1			1	1			4
	F		1								
Salmonella*	M					1		1	1		4
	F							1			
Alcaligenes faecalis	M			1				1			2
	F										
Paracolobactrum	M	1									1
	F										
Total		9	1	6	12	16	24	37	25	7	137

*Exclusive of *Salmonella typhosa*.

concentrated in the age period 30 through 69 years, for 32 of the 46 were in this age group.

Although no age group was immune, the decade 60 through 69 years represented the largest number of patients. Of 10 patients less than 20 years of age, nine were less than 10 years of age.

Portal of Entry

Review of table 2 brings out several important features of bacteremia caused by gram-negative bacilli. First, by far, is the fact that the genitourinary tract is the most common portal of entry of the offending microorganisms; this applies to both male and female patients. The gastrointestinal tract, including the biliary tract, ranks second as a portal of entry for both sexes, while in a considerable number of patients (about a sixth) no definite portal could be incriminated. The skin served as the portal of entry in only one case, a child who had been severely burned and whose burns became infected and ostensibly served as a portal of entry for *Ps. aeruginosa.*

Table 2

Distribution of Patients According to Portal of Entry of Causative Organism

Organism	Genitourinary tract				Gastrointestinal tract				Skin	Unknown
	Surgical		Nonsurgical		Surgical		Nonsurgical			
	M	F	M	F	M	F	M	F		
E. coli	19	2	14	9	7	7	6	4		8
A. aerogenes	11	1	2	4	4					2*
Proteus	3	2	3		1			1		4†
Ps. aeruginosa	5	1							1	5
Bacteroides					1	1				2
Salmonella	1						1			2
A. faecalis			1							1
Paracolobactrum							1			

* One case followed amputation.
† One case followed a nasal operation.

The second important fact is that in half of the cases (68 of 137) the bacteremia was preceded by an operative procedure; in addition, when either the genitourinary tract or the gastrointestinal tract was the portal, an operation preceded the bacteremia in more than half the cases.

In table 3 the cases in which an operation preceded the bacteremia are arranged according to the procedure undertaken. The most common operation followed by bacteremia due to a gram-negative organism was transurethral prostatic resection; this was especially true of bacteremia due to coli-aerogenes organisms. Cystoscopy ran a close second to transurethral resection, and the 18 cases that followed cystoscopy were rather evenly distributed according to four organisms: *E. coli, A. aerogenes,* proteus and *Ps. aeruginosa.*

Among operative procedures on the gastrointestinal tract, those on the biliary tract were the precursor to bacteremia in eight instances, appendectomy in five, gastric operations in three and other procedures in four.

The occurrence of bacteremia due to *E. coli* in four patients with hepatic cirrhosis was the subject of a report by Whipple and Harris,[6] who postulated that the deficiency of effective reticuloendothelium or the changes in the hepatic circulation of the cirrhotic patient might account for this. In four of the 137 cases in our series the patients had hepatic cirrhosis; *E. coli* was the offending microörganism in three cases and salmonella (species ?) in one case.

TABLE 3

Distribution of Patients According to Operation Preceding Bacteremia

Operation	*E. coli*	*A. aerogenes*	Proteus	*Ps. aeruginosa*	Bacteroides	Salmonella
Transurethral resection	10	8	1	1		1
Cystoscopy	5	4	4	5		
Catheterization	2					
Cystectomy	2					
Nephrectomy	1					
Ureterostomy	1			1		
Biliary	6	1	1			
Appendectomy	2	2			1	
Gastric	3					
Resection of colon	1				1	
Whipple resection	1					
Hemorrhoidectomy	1					
Amputation		1				
Nasal			1			

More striking in the present series was the occurrence of bacteremia due to gram-negative bacilli in patients with diabetes mellitus. Fourteen of the 137 patients were diabetic, and in all but one of these the portal of entry was the urinary tract.

CLINICAL FEATURES

In table 4 some of the more important clinical features of the cases of bacteremia are recorded. All patients were febrile, and temperatures ranged from 100° to 106° F. and were usually of a spiking nature. The onset of bacteremia was manifested by fever and chills in 92 patients, by spiking

fever without chills in 38 patients, and by fever with sudden circulatory collapse in seven patients.

All patients showed some degree of malaise, while anorexia, headache and sweating were present in many. Vomiting and stupor occurred in some cases. The pulse rate was usually elevated in proportion to the fever.

Leukocytosis was present in most cases, the most notable exception being a case of bacteremia owing to *Ps. aeruginosa,* wherein agranulocytosis and thrombocytopenia occurred. In another case of *Ps. aeruginosa* bacteremia there was thrombocytopenia. The unusual blood changes seen in bacteremia due to pseudomonas have been reported by others.[7, 8]

TABLE 4

Distribution of Patients According to Selected Clinical Features

Organism	Fever			Metastatic abscess
	With chills	Without chills	With shock	
E. coli	47	23	6	5 (1 subdiaphragmatic after biliary operation, 2 hepatic, 1 empyema and pneumonia, 1 bronchopneumonia)
A. aerogenes	18	5	1	2 (1 meningitis, 1 hepatic and pneumonia)
Proteus	11	3		2 (1 renal, 1 meningitis)
*Ps. aeruginosa**	8	4		2 (1 finger, 1 renal)
Bacteroides	3	1		2 (1 empyema and lung, 1 subdiaphragmatic after appendectomy)
Salmonella	3	1		
A. faecalis	2			
Paracolobactrum		1		1 (hepatic)
Total	92	38	7	14

* Additional features: one patient had leukopenia, thrombocytopenia and ecthyma; another had thrombocytopenia and ecthyma.

Pseudomonas bacteremia is notable in another respect: in some cases there are typical skin lesions which have been termed "ecthyma gangraenosum." These lesions were first described by Barker [9] in 1897, and have been stressed by Stanley [10] and by Geppert and co-workers.[11] These skin lesions begin as macules or vesicles, become pustular and eventually slough to form necrotic ulcers. Typically, these lesions are seen in the anogenital region and axillae. Biopsy of the lesions may reveal bacilli in the walls of the vessels, and culture may yield *Ps. aeruginosa.* Two of the 12 patients in our series with bacteremia due to *Ps. aeruginosa* had such ecthymatous lesions.

In an occasional case of bacteremia a soft systolic precordial murmur was heard initially, raising the question of endocarditis. In these cases, however, the murmur usually disappeared when the fever subsided.

The occurrence of metastatic abscesses in cases of bacteremia has been noted by others.[12] Abscesses occurred in 14 of our 137 cases, although in two of these cases the abscesses were subdiaphragmatic and followed intra-abdominal surgical procedures (table 4).

Bacterial Sensitivity to Antibiotics

The sensitivity of *E. coli* to various antibiotic agents was determined in 62 of the 76 cases. In 51 of the 62 cases the organisms were sensitive to streptomycin, and in the remaining cases they were insensitive. In 46 of 47 cases in which tests were done, the organisms were sensitive to the tetracycline group of antibiotics. Two patients afflicted with *E. coli* that were sensitive to streptomycin died despite what is generally regarded as adequate therapy with that agent. Two patients who had, in the blood stream, organisms that were sensitive to the tetracycline group also died despite adequate therapy with one of those agents. No patient succumbed, however, whose organism was sensitive to both streptomycin and the tetracycline group. The three fatalities in the group of patients receiving combined treatment with streptomycin and a member of the tetracycline group were associated with organisms that were insensitive to one or both agents.

In 23 of the 24 cases of bacteremia owing to *A. aerogenes,* the sensitivity to streptomycin was determined. In 19 of the cases there was resistance to this agent. In 19 of the 24 cases the sensitivity of the organisms to the tetracycline group of compounds was tested, but in only four cases was there resistance to this group of antibiotics. Streptomycin alone was given to five patients, of whom the two who harbored microörganisms sensitive to streptomycin recovered; in the other three patients, whose organisms were insensitive to streptomycin, adequate therapy with streptomycin did not prevent death. Of nine patients treated with one of the tetracycline group of antibiotics, all recovered. The bacilli of these nine patients were sensitive or resistant to the tetracycline compounds as follows: sensitive, six cases; resistant, two cases; not determined, one case. Of six patients receiving combined streptomycin-tetracycline therapy, the organisms were sensitive to the tetracycline group in four cases and resistant in two cases; in five of the six patients the organisms were resistant to streptomycin, including the two strains that were resistant to the tetracycline group of compounds. Notwithstanding this resistance to streptomycin in five cases, with coincident resistance to the tetracycline group in two of the five cases, all six patients treated with a combination of streptomycin and a member of the tetracycline group recovered. In three cases, use of polymyxin B sulfate (Aerosporin sulfate) was resorted to because the *A. aerogenes* re-

sisted the more commonly used antibiotics; all three of these patients recovered.

The organisms of 11 of the 14 patients afflicted with proteus bacteremia were tested for antibiotic sensitivity. One of six strains of proteus organisms tested was sensitive to streptomycin; the remaining five strains were resistant to streptomycin, and four of these were also resistant to the tetracycline group. The sensitivity of the organisms to the tetracycline group was determined in nine instances, and in all of these the organisms were resistant to these agents. Treatment with streptomycin alone was successful in the patient whose organism was sensitive to streptomycin; however, in one of five patients whose organisms were resistant to streptomycin, death followed therapy with streptomycin alone, whereas recovery occurred in two who received combined streptomycin-tetracycline therapy and in one who received a member of the tetracycline group alone. The fifth patient, whose bacteremia was due to an organism that was resistant to streptomycin, died before adequate therapy was given. All seven patients treated with a combination of streptomycin and a member of the tetracycline group recovered, despite the fact that their organisms were resistant to the tetracycline group of agents in all seven cases, and, coincidentally, were resistant to streptomycin in two of the cases.

The organisms isolated from seven of the 12 cases of bacteremia due to *Ps. aeruginosa* were tested for antibiotic sensitivity. Resistance to both streptomycin and the tetracycline group of antibiotics was found in two patients of the seven, and in one of the two there was also resistance to polymyxin. The sensitivity to polymyxin alone was determined in five cases, and the organisms proved resistant in four; of the four cases, therapy with this drug alone resulted in recovery in three, while therapy with a member of the tetracycline group plus streptomycin resulted in recovery in the other. The patient afflicted with *Ps. aeruginosa* sensitive to polymyxin recovered on therapy with streptomycin and a member of the tetracycline group. In the two cases in which the bacteremia was due to organisms that were resistant to streptomycin and the tetracycline group, successful therapy consisted of the use of a tetracycline agent alone in one case, and of a tetracycline agent in combination with streptomycin in the other.

The bacteroides organisms isolated from three cases were found to be sensitive to the tetracycline group of compounds. Therapy with a tetracycline agent in two of these cases and with a tetracycline agent plus streptomycin in the other resulted in recovery.

The sensitivities of the organisms were determined in three of the four cases of bacteremia caused by salmonella organisms. In two cases the organisms were resistant to streptomycin but sensitive to tetracycline agents. In the other case they were sensitive to streptomycin; however, therapy with streptomycin alone was unsuccessful. In the two cases in which the organisms were resistant to streptomycin but sensitive to tetracyclines, the use of streptomycin and a tetracycline agent in combination resulted in

recovery. In retrospect, the use of streptomycin in the latter two cases may have been unnecessary.

In one case the sensitivity of *Alcaligenes faecalis* was determined. The organisms were sensitive to both streptomycin and the tetracyclines, and combination therapy was successful.

TABLE 5
Distribution of Patients According to Results of Treatment

Organism	Outcome*	Therapeutic agent						
		None	Inadequate	Sulfonamides	Streptomycin	Tetracyclines	Combination	Polymyxin
E. coli	R	1	4	5	13	10	24	
	D	4	8		2	2	3	
A. aerogenes	R		1		2	9	6	3
	D				3			
Proteus	R				3	1	7	
	D		1	1	1			
Ps. aeruginosa	R				2		3	3
	D				1	1	2	
Bacteroides	R			1		2	1	
	D							
Salmonella	R				1		2	
	D				1			
A. faecalis	R				1		1	
	D							
Paracolobactrum	R						1	
	D							

Totals: recoveries, 107; deaths, 30.

* R, recovery; D, death.

The paracolobactrum isolated from one patient was found to be sensitive to streptomycin, the tetracyclines and polymyxin B. The patient recovered on treatment with streptomycin and a member of the tetracycline group. However, two months later, bacteremia due to the same organism recurred; the same therapy was again successful.

TREATMENT AND RESULTS

In bacteremia owing to *E. coli*, 40% of the 39 patients in Jacob's [13] series (1909) and 32% of the 28 patients in Felty and Keefer's [12] series

(1924) died. A mortality rate of 35.7% was noted by Herrell and Brown [1] for patients not treated with sulfonamide compounds, while the rate was 21.4% for those patients who were treated with such compounds. The Committee on Chemotherapeutics [14] in 1946 reported a mortality rate of 23.5% in 34 cases of bacteremia due to *E. coli* and treated with streptomycin.

Table 5 gives the results of treatment in our series of 137 cases. In the 76 cases of bacteremia due to *E. coli* there were no deaths among the five patients who received sulfonamide therapy alone, but this form of therapy is not so efficacious as would appear from the present group; this is evident when a larger number of patients is studied, as was done by Herrell and Brown.[1] Combined therapy with one of the tetracycline drugs and streptomycin appears to be the best form of therapy. Streptomycin alone appears to have been the next best form of therapy in this series but, as noted previously, results with larger groups of patients [14] have indicated that the agent is not so efficacious as it seems here.

In bacteremia owing to *A. aerogenes,* Keefer and Hewitt,[15] using streptomycin alone, reported a fatality rate of 26%. The results of treatment of such infection in our group of 24 cases are given in table 5. We hesitate to draw definite conclusions regarding treatment of this type of bacteremia because of the paucity of cases studied. However, tetracycline, polymyxin and combinations of streptomycin with a tetracycline drug have all been effective in our hands. Our results with streptomycin alone have paralleled the experience of Keefer and Hewitt, and we cannot recommend it.

For the 48 cases of bacteremia due to proteus organisms which Abrams [16] reviewed in 1948, the mortality rate was 64.6%. Early in the so-called streptomycin era it appeared that this form of bacteremia could be controlled by streptomycin, but the relapse rate proved to be high.[17] Armstrong and Larner,[17] on the basis of work in vitro and also on the basis of in vivo experiments in mice, reported that bactericidal effects on proteus organisms were enhanced when combinations of various antibiotics were used. In our series, combined streptomycin and tetracycline therapy was effective in seven cases of bacteremia due to this organism. As will be discussed more fully later, the response to combined therapy with streptomycin and tetracycline constituted what might be termed a therapeutic paradox because inhibition tests (in vitro) indicated that the organisms would be resistant to this form of therapy. One patient recovered after use of a tetracycline drug alone, and two of three patients recovered after the use of streptomycin alone. One patient succumbed after the use of a sulfonamide alone.

Frank and his associates [18] found polymyxin B sulfate to be the most effective agent against *Ps. aeruginosa* in vitro. Erwin and co-workers [19] recently found all strains of *Ps. aeruginosa* tested to be sensitive to the action of this agent. Our clinical experience parallels that of these workers. Stanley [10] stated that bacteremia owing to *Ps. aeruginosa* had been almost uniformly fatal, while Keefer and Hewitt,[15] in reviewing the efficacy of

streptomycin in the treatment of bacteremia due to this organism, noted a mortality rate of 50%. Jawetz [20] has recommended polymyxin B sulfate for bacteremia due to *Ps. aeruginosa,* and Geppert and associates [11] have urged the use of this agent for severe infections due to this organism. The results in our series are given in table 5. None of the three patients who received polymyxin B sulfate died. Streptomycin was used successfully in two of the three cases, but it is evident from the larger series of Keefer and Hewitt [15] that the mortality rate with such treatment is high. One patient who received only a tetracycline drug died. Combined streptomycin-tetracycline therapy was not successful in two of five cases.

McVay and associates [21] reported recovery in two cases of bacteremia due to bacteroides organisms following therapy with a tetracycline compound. Streptomycin is of little value in such infections, and there is a

TABLE 6

Conditions Associated with Fatal Bacteremia

Organism and Deaths	Associated Conditions
E. coli (19)	Carcinoma of pancreas (2 cases), carcinoma of urinary bladder (2 cases), bilateral pyelonephritis (2 cases), necrotizing papillitis, congenital aortic stenosis, carcinoma of stomach, generalized peritonitis, pylephlebitis, posthepatic cirrhosis, acute leukemia, hypernephroma, carcinoma of prostate, lymphosarcoma, choledocholithiasis, unknown (2 cases)
A. aerogenes (3)	Chronic pyelonephritis, metastatic carcinoma of prostate, carcinoma of common bile duct
Ps. aeruginosa (4)	Carcinoma of urinary bladder and pulmonary embolus, third-degree burns, cerebrovascular accident, agranulocytosis
Proteus (3)	Pyelonephritis (2 cases), grade 4 epithelioma of nose
Salmonella (1)	Hepatic cirrhosis

high incidence of in vitro resistance of the organisms to this agent. Successful therapeutic results associated with the use of sulfonamides have been described. In the past, bacteremia due to these organisms has had an extremely poor prognosis, as attested by Brown and co-workers,[22] who reported only one recovery in 15 cases. Of the four patients in our series, one responded to sulfonamide therapy and one responded to combined streptomycin-tetracycline therapy; the other two patients recovered after treatment with a tetracycline compound alone.

Of the four patients with bacteremia due to salmonella organisms, one recovered and one died after treatment with streptomycin alone; the other two recovered after combined therapy with a tetracycline compound and streptomycin. Of the two cases of bacteremia due to *A. faecalis,* one each recovered after streptomycin therapy alone and after combined therapy with

a tetracycline compound and streptomycin. In the single case of bacteremia owing to paracolobactrum, recovery followed combined streptomycin-tetracycline therapy.

Associated Conditions in Fatal Bacteremia: A better evaluation of therapy in this series of cases is obtained by a study of the associated conditions in the 30 fatal cases, as listed in table 6. It is obvious that the deaths listed were in patients with serious associated conditions, and in many instances the associated condition itself was incurable and responsible for the death.

Comment

E. coli is the most common gram-negative bacillus to invade the blood stream. In our series, about 60% of the patients with bacteremia due to gram-negative bacilli had the genitourinary tract as the portal of entry. The gastrointestinal tract, including the biliary passages, served as the portal of entry in about 25% of such cases. In about 15% the portal of entry was not recognized. In chronic debilitating diseases such as carcinomatosis, gram-negative bacilli may be obtained on culture of the blood shortly before death. In about 50% of our series of 137 cases the bacteremia was associated with an operative procedure performed on either the gastrointestinal tract or the urinary tract; in about a third of these surgical cases the procedure was concerned with the gastrointestinal tract, and in about two thirds it was concerned with the urinary tract.

We are attempting at the present time to utilize the probable synergistic effect of combined treatment with streptomycin and a compound of the tetracycline group in bacteremia due to gram-negative bacilli with the exception of *Ps. aeruginosa.* We use 1 gm. of streptomycin intramuscularly every 12 hours and 0.75 gm. of the tetracycline compound orally every six hours. (In such treatment, dihydrostreptomycin may be substituted for streptomycin or, preferably, equal parts of each may be used.) Treatment should be continued until three successive negative blood cultures have been obtained and the patient remains afebrile for 72 hours. Since these infections usually subside within two weeks, there is little danger of encountering toxic effects from the use of streptomycin in this amount in the presence of normal renal function. It would appear that any one of the members of the tetracycline group of compounds may be used. In our hands, chlortetracycline (Aureomycin), oxytetracycline (Terramycin) and tetracycline are equally efficacious. We have not noted any great differences among the members of the group as far as toxic effects are concerned.

Our practice has been to initiate antibiotic therapy empirically, in most instances, on receipt of reports of positive blood cultures from the section of bacteriology. If in vitro inhibition tests have indicated that our choice of treatment has been a poor one, we have attempted to reëvaluate the program. This explains the apparent discrepancies in our series wherein in

vitro data would indicate that one antibiotic is the agent of choice, yet we successfully used another. If the patient appears to be improving on the regimen being followed, we do not change his program merely because so-called sensitivity tests would indicate selection of another agent. For example, early in our experience with proteus bacteremia [5] it became apparent that patients were responding to a method of treatment which inhibition tests in vitro indicated would not be effective. Since the patients were doing well on combined streptomycin-tetracycline therapy, despite inhibition tests in vitro giving results to the contrary, we continued to use that method of treatment. It is apparent that thus far this method of treatment is successful. An exact explanation of the discrepancy between in vitro and clinical data has not been forthcoming. We have not been able to demonstrate a bactericidal effect of the patients' serums containing the combination of antibiotics when tested against various pseudomonas organisms.

Polymyxin B sulfate must be used with utmost caution. It has constant application, at present, only in cases of infections due to *Ps. aeruginosa,* although it is of value in refractory cases of bacteremia owing to *A. aerogenes.* Frequently, pain at the site of injection is severe. As with streptomycin and dihydrostreptomycin, acral and circumoral paresthesia may occur, but it is more severe with polymyxin. Cerebellar ataxia is not an uncommon reaction to the drug. Polymyxin B sulfate, like neomycin and bacitracin, is capable of causing renal damage. One should keep a close check on the concentration of blood urea when using the drug, and should hesitate to use it at all if the blood urea is increased. The recommended daily amount of the drug for adults is 100 to 200 mg. given intramuscularly in four doses. Smaller doses proportional to body weight are given to children. We plan to employ this drug in further cases of bacteremia owing to *Ps. aeruginosa.*

Generically speaking, one is well advised to treat bacteremia due to gram-negative bacilli with one of the tetracycline group of compounds combined with streptomycin, except when the causative organism is *Ps. aeruginosa.* In the latter instance, use of polymyxin B appears justifiable.

It has been stressed previously [2] that the age of the patient, the presence or absence of debilitating disease, the site of the primary focus of infection, the virulence of the infecting microörganism and its sensitivity to various antibiotics, and the type of treatment importantly influence the prognosis in cases of bacteremia.

Summary

The gram-negative bacillus which most commonly invades the blood stream is *Escherichia coli. E. coli* and *Aerobacter aerogenes,* considered together as the "coli-aerogenes group," were the invaders in 100 of the 137 cases of bacteremia due to gram-negative bacilli in the present series. The site of origin of the bacteremia was the genitourinary tract in 60% of the

cases and the gastrointestinal tract in 25%. In about 50% of the cases an operative procedure immediately preceded the infection; in about a third of the cases associated with surgical procedures the operation had been on the gastrointestinal tract, and in about two thirds it had been on the genitourinary tract. Treatment with one of the tetracycline group of compounds combined with streptomycin was highly efficacious, except when the causative organism was *Ps. aeruginosa*. In bacteremia due to pseudomonas organisms, use of polymyxin B appears to be justifiable.

SUMMARIO IN INTERLINGUA

Inter le invasiones del fluxo sanguinee per bacillos Gram-negative, illos per *Escherichia coli* es le plus frequente. *E. coli* e *Aerobacter aerogenes*—que nos designa insimul como le "gruppo *coli-aerogenes*"—esseva le invasores in 100 del 137 casos de bacteremia a bacillos Gram-negative in le presente serie. Le sito originari del bacteremia esseva le vias genito-urinari in 60 pro cento del casos e le vias gastro-intestinal in 25 pro cento. In circa 50 pro cento del casos un intervention operatori habeva precedite le infection immediatemente. In circa un tertio del casos associate con tal interventiones, il se habeva tractate de chirurgia del vias gastro-intestinal; in circa duo tertios, de chirurgia del vias genito-urinari. Therapia con un composito del gruppo tetracyclinic in combination con streptomycina esseva efficacissime, excepte quando le organismo causative esseva *Pseudomonas aeruginosa*. In casos de bacteremia causate per *Pseudomonas*, le uso de polymyxina pare justificate.

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METACORTANDRACIN (METICORTEN) IN THE TREATMENT OF DISSEMINATED LUPUS ERYTHEMATOSUS AND PERI-ARTERITIS NODOSA *

By CHARLES LEROY STEINBERG, B.S., M.D., F.A.C.P., and ANDRIES I. ROODENBURG, M.D., M.S. (Medicine), *Rochester, N. Y.*

DISAPPOINTMENT in the long-term treatment of rheumatic diseases with cortisone and allied steroids has stimulated a search for newer compounds. Two of these compounds are metacortandracin and metacortandralone, which were recently reported as being of value in the treatment of rheumatoid arthritis by Bunim et al.[1] They recently made preliminary observations on the antirheumatic and anti-inflammatory potency of these synthetic steroids. The structural formula of metacortandracin and metacortandralone and their close relationship to cortisone and hydrocortisone are noted in the figures below. Studies [2] indicated that these compounds possessed three times the activity of cortisone and twice the activity of hydrocortisone, as measured by animal studies using the eosinophil response, liver glycogen deposition and thymus involution methods. The comparative potencies of these compounds are shown below.

	Average Daily Initial Dose	Average Daily Maintenance Dose
Cortisone	100 mg.	50 mg.
Hydrocortisone	80 mg.	40 mg.
Metacortandracin	20–30 mg.	5–20 mg.

While it was interesting that their meticulously controlled clinical, histopathologic and biochemical studies indicated that these two new synthetic hormones possessed both antirheumatic and anti-inflammatory properties, a most valuable observation was that, when patients with rheumatoid arthritis were given sufficient amounts of these hormones to suppress the arthritis completely, no retention of sodium and no loss of potassium occurred. No disturbance of glucose metabolism was noted. Slight nitrogen loss occurred if the protein intake was limited.

The advantages of these new corticoids over cortisone and similar compounds are the following:

1. Avoidance of sodium retention.
2. Absence of potassium depletion.
3. Anti-inflammatory activity, supposedly three to four times that of either cortisone or hydrocortisone.

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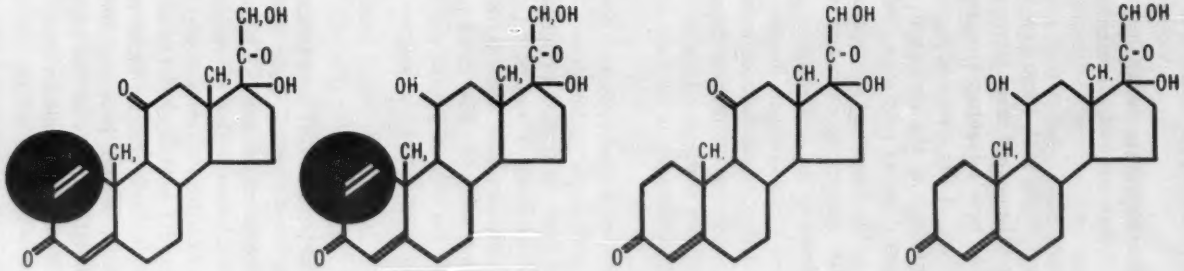

METICORTEN
(prednisone, Schering, formerly metacortandracin)
($\Delta^{1,4}$-pregnadiene-17α, 21-diol-3, 11, 20-trione)

METICORTELONE
(prednisolone, Schering, formerly metacortandralone)
($\Delta^{1,4}$-pregnadiene-11β, 17α, 21-triol-3, 20-dione)

cortisone
(11-dehydro-17-hydroxycorticosterone)

hydrocortisone
(17-hydroxycorticosterone)

FIG. 1.

4. Little, if any, disturbance of protein metabolism in the usually accepted dosage.

5. No proved disturbance of carbohydrate metabolism as yet.

6. Less production of such other untoward reactions as hirsutism, moonface and gastric disturbances.

It must be pointed out that experience with these new hormones is very limited as compared to that with cortisone and other steroids. It is possible that, with added experience, either new advantages or new complications will result from their use. However, if the above advantages hold true, it would seem best to use these hormones in the treatment of the malignant collagen diseases where much larger doses of cortisone (and therefore more complications) are required than in the treatment of rheumatoid arthritis.

It is a well known fact that the amount of cortisone or hydrocortisone usually required as maintenance doses in the treatment of patients with disseminated lupus erythematosus and other collagen diseases is so high that it is almost impossible to maintain electrolytic balance between sodium and potassium. Because of this fact, and the interesting results noted by the above investigators in the treatment of rheumatoid arthritis, we decided to study patients with various collagen diseases as to their response to metacortandracin.*

Six cases of disseminated lupus erythematosus and three patients with periarteritis nodosa were treated with metacortandracin. The diagnosis of disseminated lupus erythematosus was confirmed in all incidences by the finding of L.E. cells both in the bone marrow and in a two hour clot test. Two of the patients with periarteritis nodosa were confirmed by biopsy, and in one instance also by autopsy studies. The third patient with periarteritis nodosa had no biopsy, but his clinical course was so typical of the disease that there appears to be no question of the diagnosis.

Method of Study

With the exception of case 9, all patients had been treated with cortisone or hydrocortisone at some time in their illness. Four of the patients were shifted directly from cortisone to metacortandracin. This shift was possible without any break in the therapeutic effectiveness of metacortandracin. In other words, the flare-up of the rheumatic syndrome which usually occurs after cessation of cortisone therapy did not occur. The following observations were made at frequent intervals: body weight, blood pressure, circulating eosinophils, sedimentation rate, serum proteins, including albumin, globulin and gamma globulin, cellular elements of the blood, blood sugars, blood cholesterols, cholesterol esters and serum electrolytes.

Body Weight: All patients were weighed weekly or oftener, either in

* Metacortandracin made available to us by Dr. E. L. Henderson, of the Schering Corporation.

the hospital or in the clinic. The weight variations of these patients are given in the table below.

A normocytic hypochromic anemia was present in three cases. This anemia responded to metacortandracin without the use of iron salts. Leukopenia of 1,300 responded dramatically to this therapy after cortisone in doses of 150 mg. per day had failed. Sporadic platelet counts were done both before and after therapy and were always within normal range.

Either bone marrow or two hour clot tests for L.E. cells were done at frequent intervals in all of the L.E. cases. In no instance did these cells disappear for any length of time. Our own observation is that L.E. cells will appear in a greater or smaller amount depending upon the particular day on which the preparation is made. It apparently has no relationship to the clinical status. Various time intervals have been used on the so-called "two hour" clot test; as a matter of fact, we waited up to 48 hours and found no particular difference in either the abundance or the scarcity

TABLE 1

Case	Initial Weight		1st wk.	2nd	3rd	4th	5th	6th	7th	8th	9th
1	116.5	Metacortandracin Started	116	117	118	116	116	117	118	118	120
2	118½		117	116	119	120½	124	123	125	123½	124
3	115		118	124	122½	125	125	125	126½	126	126
5	119		115								
6	187		190½	186	189¾	187	188¾	188½	189½	186½	184
4	113¾					119½					
8*	161		161½	161	160	162	161½	164	163	163½	163
7*											
9*											

* Periarteritis; others, disseminated lupus erythematosus.

of the so-called L.E. cell phenomenon. At other times, a marked increase in L.E. cells is found if the preparation is examined 24 to 48 hours later.

Blood Sugars: Blood sugars were taken on all of these patients at various intervals. In no instance were there any findings to suggest that metacortandracin leads to the development of hyperglycemia, and in two diabetic patients in whom metacortandracin was used there was nothing to indicate that the insulin requirement had been increased. More experience will be required before it can be said definitely that metacortandracin does or does not alter carbohydrate metabolism.

Blood Cholesterol and Cholesterol Esters: In four patients the blood cholesterol remained relatively unchanged but there was a concomitant rise in the blood cholesterol esters. The significance of this change is unknown.

Circulating Eosinophils: A prompt and rapid drop of the circulating eosinophils was characteristic when patients were placed on metacortandracin. The circulating eosinophils were much lower with the larger doses of 30 mg. per day than in those instances in which the dose had been lowered

to 15 mg. per day. The circulating eosinophils followed an erratic course while the patients were on steroid therapy. It was not uncommon to find the circulating eosinophils varying markedly from day to day, but they were always lower during steroid therapy than if no steroids were given. It appears that the response to steroids is more sensitive if they are given to a patient who has not previously received such hormones. A large dose of steroids given suddenly to such a person will cause a marked drop in the circulating eosinophils, whereas the response is less in those who have been taking steroids for some time.

Sedimentation Rate: None of the patients with disseminated lupus erythematosus or periarteritis nodosa had a return to normal of the sedimentation rate while under this treatment. When we ran a series of rheumatoid arthritis patients we found that with the same dose the sedimentation rate

TABLE 2
Cholesterol/Cholesterol Esters

Case	Initial		Date				
1		Metacortandracin Started					
2	12-8-54 176/72		1-19-55 150/66	2-2-55 147/71	4-6-55 175/109		
3	1-7-55 161/51		1-21-55 182/64	1-25-55 182/72	2-9-55 161/83	3-2-55 162/82	4-6-55 184/90
5							
6							
8	2-7-55 183/57		2-15-55 195/67	3-2-55 218/133	3-16-55 237/125	4-6-55 236/137	
7	1-12-55 142/78		1-19-55 142/47				

dropped to normal. Perhaps if doses larger than 30 mg. a day were used, there would be a drop in the sedimentation rate.

Blood Proteins: Blood protein studies were done at frequent intervals while the patients were under treatment. There was no clear cut pattern showing a return to normal of the blood proteins, although the gamma globulin eventually lowered after weeks of treatment. Perhaps larger doses would have shown more definite results.

Serum Electrolytes: Blood serum sodium and potassium studies were done, usually at weekly intervals. In no instance did the blood potassium drop. In case 2 a mild hypopotassemia of 3.5 to 3.9 mEq. was almost always present over a five year period while the patient was on cortisone therapy. This hypopotassemia was not responsive to doses of potassium chloride of up to 6 gm. daily. One week after metacortandracin therapy, and with

no added potassium, the serum potassium returned to normal and has remained normal ever since. The electrolyte studies in three cases are summarized in figure 2.

Nonprotein Nitrogen: All cases of periarteritis nodosa had an increase in their nonprotein nitrogen at some time during this study. A return to normal occurred in the two living cases. Two patients with disseminated lupus erythematosus have had persistently elevated nonprotein nitrogen. One of these two cases became pregnant while the study was being carried out. The new steroid had no effect, either beneficial or malevolent, on the azotemia.

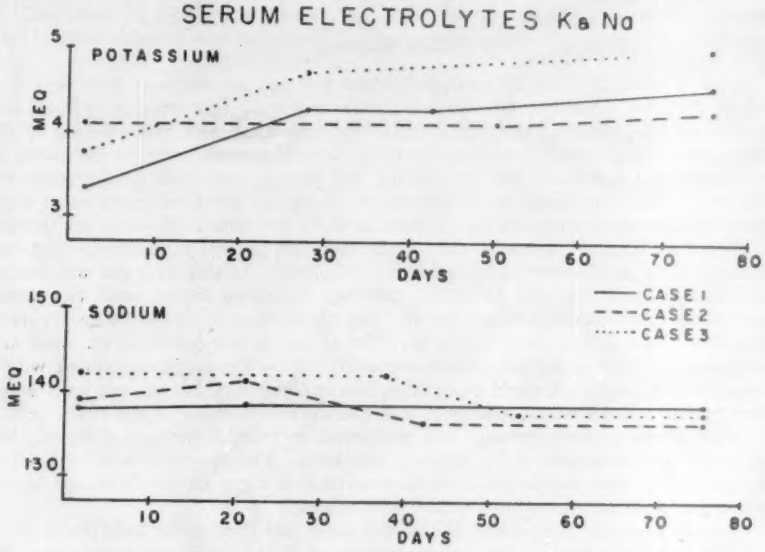

FIG. 2. Note rise in serum potassium and drop in serum sodium during days of treatment with metacortandracin.

Urinalysis: Renal damage is common as part of the pathology of both disseminated lupus erythematosus and periarteritis nodosa. Six cases of this series had albuminuria ranging from a trace to 3 plus. The nonprotein nitrogen was elevated in five cases. The renal damage was associated with hypertension in three cases. The blood pressure readings in these cases were: case 3, range, 170/90 to 210/150 mm. of Hg; case 6, range, 160/100 to 176/100 mm. of Hg; case 8, range, 160/120 to 190/140 mm. of Hg. The blood pressure remained normal throughout metacortandracin therapy in three other cases, and became elevated to 150/120 mm. of Hg in the three year old case 7 several days before death. There was no significant effect of treatment on the blood pressure.

Tumulty [8] noted that 69 of the 105 reported cases of lupus erythematosus

showed some type of abnormality of the urinary tract. Forty-one patients had a mild degree of involvement, 24 moderate to severe kidney damage, and 12 died of uremia. He noted that cortisone and corticotropin had little effect in reversing the renal alterations. The same can be said of metacortandracin in our series of cases. The albuminuria waxed and waned in six cases, but over a period of weeks did not seem to show any particular change. Also, there was no remarkable change in those who had azotemia. Albuminuria and azotemia may disappear spontaneously with or without the use of steroids. At least there is nothing to indicate that metacortandracin has any specific effect upon the renal abnormalities that have been found.

Case Reports

Case 1 (*L.E.*). This 36 year old white married woman was first seen November 29, 1954. She had first become aware of a gradual increasing stiffness and generalized body aches in August, 1954. Angioneurotic edema and swelling of the fingers were also noticed from time to time. Poorly defined areas in the palms of the hands and the soles of the feet felt hot and painful, and some discoloration was observed. These symptoms were relieved by 25 mg. of cortisone given every eight hours. When this medication was discontinued by her family physician on October 4, 1954, the "bruised" areas on her hands and feet promptly recurred. She was hospitalized for two weeks beginning October 6, 1954. At that time she was treated with aspirin, penicillin and Pabalate. She felt somewhat better until two weeks prior to the consultation of November 29, 1954, at which time her symptoms recurred. In addition, she had a continuously sore throat and a low grade fever. She also complained of pain in the left posterolateral portion of her chest, associated with a nonproductive cough. A chest x-ray taken late in October, 1954, was not remarkable. Her appetite had decreased, and there was intermittent swelling of the ankles.

Past History: Tonsillectomy was performed in 1926 at the age of eight. She had a convulsive episode at 13, etiology unknown. The appendix was removed at the age of 17. She complained from time to time of right supra-orbital and nuchal headaches; these were associated earlier with nausea.

Family History: Both the mother and a sister had rheumatoid arthritis.

Physical Examination: The salient feature of the physical examination was her appearance of chronic illness but good nutritional status. Her nude weight was 124 pounds; height, 5 feet 2 inches; temperature, 99.8° F.; pulse, 80; blood pressure, 114/78 mm. of Hg. The face was edematous. The left occipital lymph nodes were palpable. A grade 1 systolic murmur was heard at the apex in the supine position. An abdominal scar as a result of an appendectomy was noted. The third right metacarpophalangeal joint was slightly swollen. Fluoroscopic examination of the chest and the electrocardiogram were not remarkable.

Laboratory Examinations: Urine: Clear, acid; specific gravity, 1.013; a slight trace of albumin was present. Microscopic examination revealed eight to 10 red blood cells and six to eight white blood cells per high power field. An occasional hyaline cast was present. Red blood cells, 3,820,000; hemoglobin 13 gm.; white blood cells, 5,050. Differential: Stabs, 3; segs, 66; lymphocytes, 30; monocytes, 1. A two hour clot showed no L.E. cells, but a few stitch cells were seen. However, two days later a two hour blood clot showed L.E. cells. The sedimentation rate was 28; hematocrit, 36; C reactive protein, 1 plus.

The patient was placed on 25 mg. of cortisone every eight hours, with supplementary potassium chloride. At first she seemed to benefit from this treatment, but

the symptoms and the swelling of the face became more severe, and on December 7, 1954, she was admitted to the Rochester General Hospital.

Course in Hospital: On December 7, 1954, the patient was placed on 25 mg. of cortisone every six hours, with supplementary potassium. However, she complained bitterly of a pleuritic type of pain in her chest, and developed a leukopenia of 1,300 and spiked a temperature of up to 103° F. The angioneurotic edema markedly increased, and she appeared to be disoriented at times. Because of this she was placed on Meticorten therapy, beginning December 23, 1954.

The leukocyte count immediately began to rise (figure 3), the temperature dropped to normal, the patient became oriented again and the pleuritic pain disappeared. The following notes from the record indicating the degree of facial edema are interesting.

December 14, 1954 (figure 4A): The facial edema was at a maximum. December 17, 1954: Patient complained of feeling water-logged, had a productive cough

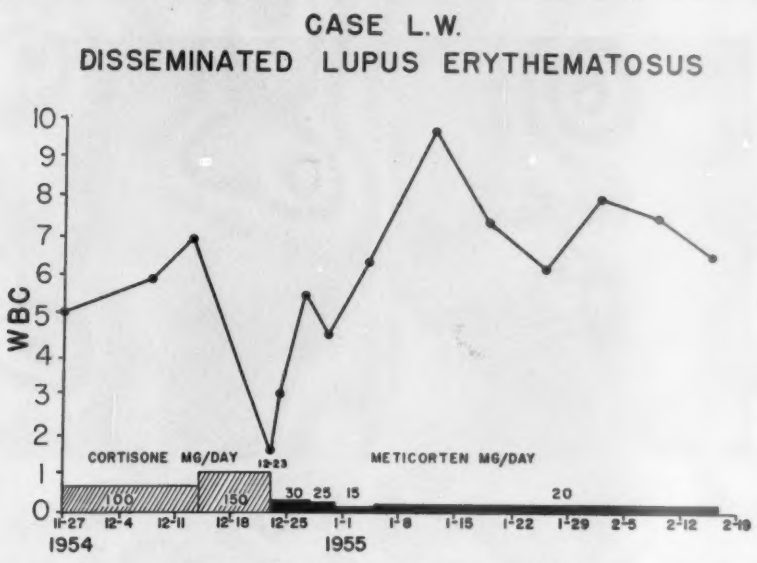

FIG. 3. Leukocyte response to metacortandracin.

and was expectorating yellow mucus. December 18, 1954: Massive periorbital edema was present. December 25, 1954: A pleural friction rub was heard by one observer over a small area of the lower one third of the posterior aspect of the right hemithorax. Facial edema was marked. December 27, 1954: The lungs were clear to percussion and auscultation. No facial edema was seen. January 1, 1955: The patient had lost one and one-half pounds and was feeling greatly improved.

There were no significant changes in her blood pressure. On December 8, 1954, x-ray study revealed a small amount of pleural effusion in both bases which was no longer present on the film taken December 23, 1954. By January 6, 1955, she had no untoward symptoms (figure 4B).

On December 8, 1954, a bone marrow examination revealed a few typical L.E. cells (figure 5). There was a large number of round nuclei that stained like L.E.

cells and tended to be homogeneous, but were not phagocytized. A few of these were less homogeneous and seemed to show the shadows of lymphocytic nuclear structure. A two hour clot contained a large number of L.E. cells. On December 20, 1954, a two hour clot showed L.E. cells or rosettes, although there was some free purple material reminiscent of L.E. inclusion. On December 22, 1954, a two hour clot was negative for L.E. cells.

During the first week of Meticorten administration there was some anemia and a marked leukopenia, which were both corrected with further Meticorten administration. The nonprotein nitrogen content decreased. There was a tendency for the serum sodium to fall, and the serum potassium rose. There were no significant changes in the sedimentation rate, the plasma proteins or the fasting blood sugar.

Case 2 (L.E.). A 17 year old white woman was first admitted to the Rochester General Hospital on June 6, 1950. For two weeks she had had painful swelling of the wrists and fingers, stiffness of the elbows, shoulders and knees, generalized muscular soreness and lassitude. She had noticed a rash covering the bridge of the nose

A B

FIG. 4. *A.* Facial edema present, December 10, 1954, before metacortandracin therapy. *B.* Clearing of facial edema on January 5, 1955, two weeks after metacortandracin therapy.

and the malar areas. She had been losing weight—20 to 25 pounds—during the last year for no apparent reason.

Past History: The patient had had otitis media at eight months, paronychia of the right index finger at 12, and cellulitis of the right upper arm at 14.

Family History: Noncontributory.

Physical Examination: The salient features were the "butterfly" rash and swelling of the proximal interphalangeal and wrist joints. Blood pressure was 105/60 mm. of Hg; pulse, 80. Laboratory examination: The bone marrow was "loaded" with L.E. cells. Red blood cells, 4,850,000; hemoglobin, 14 gm.; *white blood cells, 1,480.* Differential: Stabs, 5; segs, 63; lymphocytes, 32. The sedimentation rate was 31. Urinalysis: Specific gravity, 1.020; albumin, 1 plus; a few red and white cells per high power field. Nonprotein nitrogen, 34. FBS 93. Total serum protein, 6.7; serum albumin, 4.2; serum globulin, 2.5 gm. per 100 c.c.; cephalin flocculation, 2 plus; thymol turbidity, 3.8 units; gamma globulin, 1.33. The temperature varied between 98 and 99.6° F.

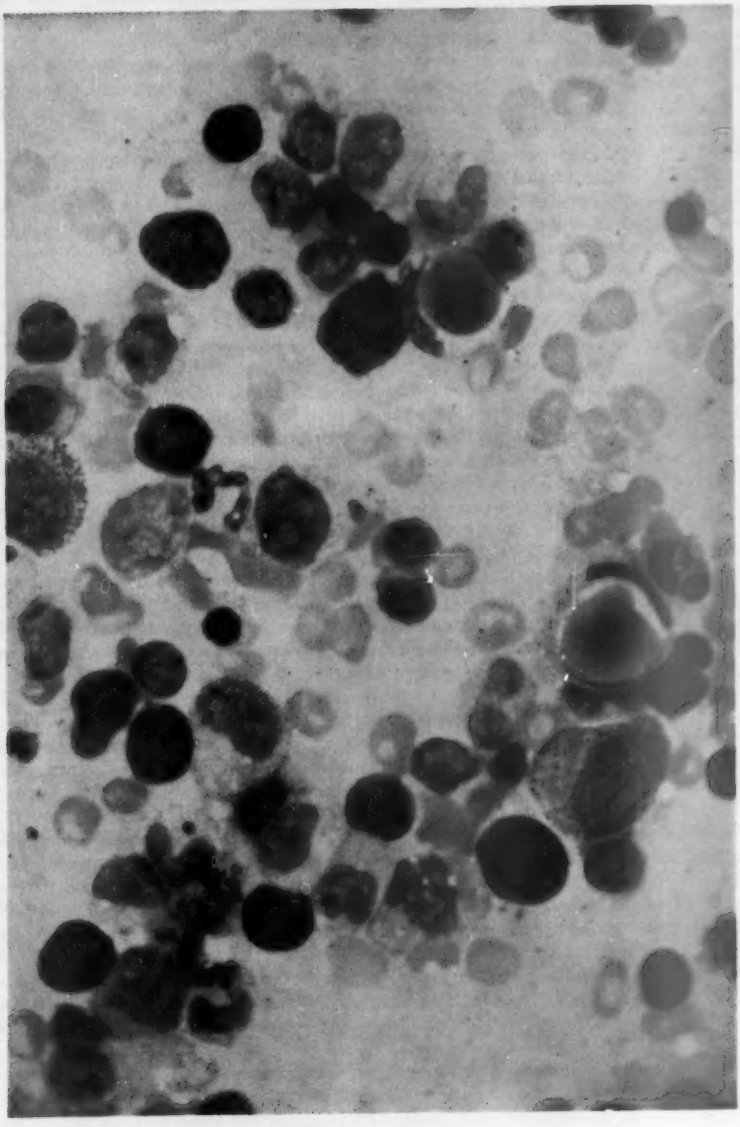

FIG. 5. L.E. cells in case 1.

Cortisone was given in the following doses: first day, 300 mg.; second day, 200 mg.; 100 mg. thereafter. The joint pain disappeared almost immediately and the temperature remained at 98.6° F. The rash faded, white blood cell count became normal, and the urine became free of albumin and cells.

The patient has been maintained on cortisone ever since, with short interruptions during which the disease promptly relapsed. At times it has had to be supplemented with ACTH intramuscularly when symptoms began to reappear, although she was receiving cortisone.

In April, 1952, the patient married. She has had two uneventful pregnancies and normal deliveries of full term babies, in 1952 and 1954, respectively.

In the summer of 1953 the cortisone had to be increased to 150 to 200 mg. daily because of increased joint symptoms and fever; this was occasionally supplemented by ACTH, 20 units intramuscularly daily.

Gradually a mild hypopotassemia (3.2 to 3.6 mEq.) developed that did not respond to administration of extra amounts of potassium chloride taken by mouth.

When the patient was seen on December 8, 1954, she was comfortable on 200 mg. of cortisone daily. In view of her unsteady course, however, it was decided to try Meticorten.

Preliminary Laboratory Examination before Starting Meticorten: Laboratory studies preliminary to Meticorten therapy showed circulating eosinophils, 121 per cubic millimeter; sedimentation rate, 41; hematocrit, 42 vol. %; fasting blood sugar, 89; serum protein, 7 gm.; serum albumin, 3.9; serum globulin, 3.1; gamma globulin, 1.475; blood cholesterol, 176; esters, 72; C reactive protein, 1 plus.

The patient was then placed on the following dosage of Meticorten: 30 mg. per day for five days, given in 10 mg. doses every eight hours; at the end of five days, the dosage was changed to 25 mg. per day.

On January 19, 1955, she was free from symptoms, was able to do all her housework without fatigue, and the joint symptoms had completely disappeared. The "butterfly" rash had faded remarkably. It was interesting that on February 2, 1955, the patient remained comfortable in spite of an intercurrent upper respiratory infection, from which she recovered without any added medication.

Case 3 (*L.E.*). This white man was first seen in August, 1953, at the age of 54. He had begun to have pain in his arms and legs two years previously. These joint symptoms subsided spontaneously after four months. He remained well until April 1, 1953, at which time he developed painful swelling of most of his joints. His appetite became poor and he lost 30 pounds. He has not been able to work since.

Past History and Family History: Noncontributory.

Physical Examination: The principal findings of the physical examination were his sallow, thin appearance (he was 40 pounds underweight), a blood pressure of 160/94, mm. of Hg and a pulse rate of 96. He had swelling and restricted motion of the small joints of both hands and both wrists, minor flexion deformities of both elbows, pain and restricted motion of the shoulders, and pain and swelling of all the metatarsophalangeal joints and both ankles.

Laboratory Examination: Urinalysis, negative; sedimentation rate, 21; hematocrit, 27; red blood cells, 3,320,000; hemoglobin, 9.5 gm.; white blood cells, 5,500. Differential: Stabs, 3; segs, 63, lymphocytes, 32; eosinophils, 2. The icterus index was 4.2.

The patient was not seen after his initial examination until October 26, 1953, when he was admitted to the Rochester General Hospital. The findings were essentially the same as those noted in August. In addition, the bone marrow was found to contain many L. E. cells. Gamma globulin, 1.77; phenolsulfonphthalein test, 38% in 60 minutes. Urea clearance, 59.4%.

The patient's temperature spiked to 102 to 103° F. until he was placed on corti-

sone, in doses of 200 mg. daily. On discharge, he was placed on a daily maintenance dose of 75 mg. of cortisone, which only partially suppressed his symptoms. He continued to have intermittent swelling and pains of various joints, and generally felt below par. At times he noticed epigastric pain as if he had a peptic ulcer. His blood pressure gradually rose.

On September 22, 1954, he was admitted to the Rochester General Hospital because of headaches and dizziness which he had had for one month. He also complained of numbness of the left forearm, which began a half-hour before admission. Blood pressure was 210/112 mm. of Hg. The right pupil was larger than the left. There was rotatory nystagmus bilaterally. His speech was thick. Electrocardiogram showed flat T waves in all leads; this, as well as the neural symptoms, disappeared upon rest in bed. The electroencephalogram and spinal fluid examination were normal.

On December 9, 1954, he was re-admitted to the hospital because of fever, dyspnea and signs of pulmonary congestion. Blood pressure, 160/100 mm. of Hg; pulse, 120; respiration, 36; temperature, 102.4° F. Bubbling râles and dullness were found in both bases. The record mentions that a gallop rhythm was heard. He was treated with penicillin, 1,200,000 units daily. The temperature became normal on the sixth day of hospitalization, and he was discharged on the ninth day, December 18, 1954.

On the evening of that day, at home, he had a burning sensation in the left hypothenar area. Subsequently, the volar surfaces of the distal phalanges of the fourth and fifth digits became painful and purple. He was seen on December 23, 1954, when a good radial pulse was felt but the ulnar pulse was absent. He made a full recovery.

On January 7, 1955, he was re-admitted to the hospital for a trial of Meticorten therapy. The remarkable points of the physical examination upon admission were: blood pressure, 186/100 mm. of Hg; pulse, 106; respiration, 20; temperature, 99.6° F. There was a soft, blowing systolic murmur at the apex which was transmitted to the axilla. The metacarpophalangeal joints of both hands were swollen.

Meticorten treatment was started on January 14, 1955. The temperature became normal. The patient felt well and became somewhat euphoric. By January 20 he had complete relief of all joint symptoms.

Case 4 (*L.E.*). When first seen, on November 24, 1954, this 32 year old white female gave a history of painful, swollen joints over a five year period. She had been treated with 75 to 150 mg. of cortisone daily during the preceding months, without relief of her joint symptoms. She had noted progressive fatigue in the past five to six years, and had run a low grade fever from time to time. The most interesting findings were those concerning her skin and soft tissue structures. There was an abnormal type of soft tissue which felt leathery and extended from the fingers proximally to the mid-arms. There was similar involvement in her lower extremities, extending from the toes to the mid-thighs. Marked vasospasm of her hands, sufficient to change from redness to actual cyanosis, was noticed during the examination. (She volunteered the information that the skin on her face had felt tight for many years.)

Her initial laboratory examination revealed the following: Urinalysis, negative. Red blood cells, 4,170,000; hemoglobin 14.2 gm.; white blood cells, 5,800. Differential: Stabs, 4; segs, 63; lymphocytes, 31; monocytes, 1; eosinophils, 1. *A two hour clot was positive for L.E. cells.* The sedimentation rate was slightly increased (to 21 mm. per hour). The C reactive protein was 1 plus. An electrocardiogram was normal.

A biopsy of the skin and muscle of the calf was essentially negative except for slight decrease in the corium. No inflammatory cells were noted. Cortisone was continued in a dose of 25 mg. every eight hours until March 16, 1955, at which time

Meticorten was started. The patient had continued to complain of joint pain and dizziness while under cortisone therapy. A two hour clot test for L.E. cells was still positive on March 16, 1955. The C reactive protein was negative.

The patient has exhibited clinical improvement on Meticorten, and when last seen (April 15, 1955) was being maintained on 20 mg. per day. Her dizzy spells had markedly diminished. The chief complaint was tender finger pads from time to time. There has been a progressive increase in her body weight while on steroid therapy. When first seen, November 24, 1954, she weighed 113 pounds. On January 29, 1955, the weight was 113¾ pounds; March 16, 1955, 119½ pounds; April 15, 1955, 124 pounds. The blood pressure has remained normal throughout.

Case 5 (*L.E.*). This white married woman was first seen in March, 1948. Her age then was 28. She had had intermittent painful swelling of one or another of the proximal interphalangeal joints since 1940. In 1945 she first developed painful swelling of the wrists, knees, feet and ankles, which had persisted. She had a five year old child, and four years before had been pregnant for the second time. This pregnancy had to be terminated because of eclampsia. The salient features of the physical examination were her weight, which was 99 pounds (standard weight, 124 pounds); swelling of the left second and third metacarpophalangeal joints, partial ankylosis of the right wrist, and painful swelling with increased local heat of the knees.

The urine contained a trace of albumin. Red blood cells, 3,840,000; hemoglobin, 10.8 gm.; white blood cells, 4,250. Differential: Stabs, 3; segs, 46; lymphocytes, 45; monocytes, 3; eosinophils, 2; basophils, 1. The sedimentation rate was 25 mm. per hour; hematocrit, 34 vol.%. Under treatment with gold salts, the patient's weight increased to about 120 pounds, and she began to feel better. When the albuminuria became more intense the gold treatment was discontinued (December, 1948). Subsequently, there was an occasional exacerbation of joint symptoms and she lost weight, staying around 110 pounds. Gold therapy was begun again in June, 1952, but discontinued on February 7, 1953, when L.E. cells were found in her bone marrow. She was given cortisone, 50 mg. per day. There was clinical improvement in her arthritis and a general sense of well being. She became pregnant again in October, 1954, with marked remission of her joint symptoms, even though she voluntarily stopped cortisone. She had a miscarriage in January, 1955. Her chief complaints when seen on February 20, 1955, were headaches. Blood pressure was 118/80 mm. of Hg. The fundi were normal. The right wrist was completely ankylosed, the left wrist partially. The metacarpophalangeal joints of the left hand were swollen, and the fingers of both hands showed the various deformities typical of rheumatoid arthritis. Urinalysis was negative. Red blood cells, 3,890,000; hemoglobin, 13.5 gm.; white blood cells, 5,900. Differential: Stabs, 4; segs, 53; lymphocytes, 40; monocytes, 1; eosinophils, 2. A two hour clot for L.E. cells was positive. The C reactive protein was 1 plus. The sedimentation rate was 36, the hematocrit, 37. The patient was placed on Meticorten therapy. There was complete subsidence of headaches when she was seen one week later. She has continued to maintain marked clinical improvement on Meticorten, a dose of 20 mg. per day.

Case 6 (*L.E.*). This 37 year old white married female was first seen when she was admitted to the Rochester General Hospital on May 21, 1952, in an L.E. crisis. She had a fever of up to 104° F. Marked pleural effusion was present bilaterally, and there was marked cardiac enlargement and tachycardia. Blood pressure, 170/110 mm. of Hg. There were albuminuria, azotemia and an inverted A/G ratio. The bone marrow was positive for L.E. cells. The patient was placed on heroic doses of cortisone (3,000 mg. daily), under which she improved. However, there was some difficulty in controlling the electrolytes, and her nonprotein nitrogen rose to 150 mg.%. She was subsequently placed on corticotropin, and was kept on small maintenance doses of this until August, 1953.

She continued to have joint pains, edema of the feet and lower extremities, and tachycardia, and her blood pressure varied from 180/120 to 130/90 mm. of Hg. Albuminuria ranged from 3 plus to 4 plus, but the nonprotein nitrogen gradually returned to normal. In spite of the gradual disappearance of the edema, her weight rose from 170 pounds on discharge from the hospital on June 14, 1952, to between 185 and 190 pounds.

From the spring of 1953 until August, 1953, corticotropin was maintained in very small doses, ranging from three to five units per day. It was discontinued in August, 1953. The patient remained essentially free from symptoms but had tachycardia, a blood pressure of around 150/100 mm. of Hg, and albuminuria. The total serum protein was 6.0 gm.; albumin, 2.8; globulin, 3.2 gm.% when she was seen in May, 1954.

The patient again came under medical observation in January, 1955. She reported that she had felt well until Christmas, 1954, when she developed a cough which lasted 10 days. During this period her temperature was elevated to 99.5° F. There was also a pleuritic type of pain in her left base. She was first placed on Meticorten on February 28, 1955. Under this medication there has been a gradual decline of her albuminuria; 3 plus on March 7, 14 and 21, 1955; 2 plus on April 4, 1955; 1 plus on April 12, 1955. Her azotemia dropped from 72 mg.% to 54 mg.% on April 12, 1955. Her blood pressure has been persistently in the range of 160 to 180 systolic and 100 to 110 diastolic. The pleuritic pain disappeared at the end of one week of Meticorten therapy.

Case 7 (*Periarteritis nodosa*). This young male was born February 18, 1952. The purpose of his fourth hospital admission on January 12, 1955, was for metacortandracin treatment. He had had three previous hospital admissions because of fever, with spikes as high as 105° F., abdominal cramps and general lassitude. These hospital admissions were on the following dates: first, August 15 to September 13, 1954; second, November 21 to December 11, 1954; third, December 13 to December 31, 1954. No definite diagnosis was made during these admissions. However, during the third hospital admission the following impressions were considered: (1) collagen disease; (2) lymphoma; (3) chronic infection; (4) neoplasm. Biopsies of lymph nodes, skin and muscle on December 23, 1954, did not help in making a conclusive diagnosis. One interesting finding during this last admission was that dissection of the brachial artery on the right side indicated an aneurysmal dilatation extending almost the entire length of the artery from the axilla down to the elbow. A diastolic aortic murmur was first noted during this admission. A systolic apical murmur had been noted during the previous periods of observation.

A conclusive diagnosis of periarteritis nodosa was made at the time of his fourth and last admission. During this admission, which lasted from January 12 to January 27, 1955, he was treated with metacortandracin in dosages varying from 15 to 20 mg. per day. When admitted he was still running a fever, with spikes ranging to 105.4° F. His temperature immediately dropped to normal, except for one day (January 24, 1955) when it rose to 103° F. His appetite improved and he appeared more cheerful. During this admission a biopsy of one of the blood vessels in the occipital area showed evidence of periarteritis nodosa. Unfortunately, it was taken after he had been on metacortandracin therapy for several days. It was interesting to see the lack of inflammatory reaction. The size of the nodular character of this artery decreased at least 50% during the four days of metacortandracin therapy before the biopsy was taken. He continued to have abdominal cramps from time to time while on metacortandracin. His blood pressure during one period of observation in the hospital rose to 155/120 mm. of Hg. The laboratory work while he was on this medication is summarized in table 4. He was discharged from the hospital on 15 mg. of metacortandracin daily.

The patient was re-admitted to the hospital on January 28, 1955, with generalized

convulsions. The following day he was unable to move his right arm or right leg. However, on January 30, 1955, he had complete return of motor function and no residual of the episode. He was discharged from the hospital January 31, 1955, on 15 mg. of metacortandracin daily. He was last seen in the Out Patient Department of the Arthritic Clinic on February 9, 1955, at which time he had no fever and practically no abdominal symptoms. His appetite was no longer a problem. He weighed 25 pounds. Blood pressure was 130/? mm. of Hg. On the morning of February 14, 1955, he awoke with severe abdominal cramps, became comatose and died within a short period.

A summary of his blood proteins during his various admissions follows:

TABLE 3

Protein Studies

	Patient	Normal Range
August 26, 1954		
Jacox protein values	6.15	6.5–8.0
Serum albumin	2.7	4.5–5.5
Total globulin	3.45	2.0–3.1
Alpha 1 and 2	0.9	0.7–1.0
Fibrinogen	0.85	0.3–0.45
September 7, 1954		
Total protein	7.1	6.5–8.0
Albumin	3.2	4.5–5.5
Total globulin	3.9	2.0–3.1
Alpha 1 and 2	2.2	0.7–1.0
Beta and gamma	1.7	1.5–2.0
Fibrinogen	0.82	0.3–0.45

FIG. 6. *Case 7.* Marked thickening of hepatic arteries.

FIG. 7. *Case 7.* Marked thickening of renal arteries.

TABLE 4

Other Laboratory Studies during Meticorten Therapy (case 7):

January 12, 1955: Nonprotein nitrogen, 28; hematocrit, 34 vol. %; sedimentation rate, 16; glucose, 85; total protein, 7.2; serum albumin, 4.0; serum globulin, 3.2; cholesterol, 142; cholesterol esters, 78.

Two hour clot showed no L.E. cells.

Gamma globulin, 1.326.

Red blood cells, 5,220,000; hemoglobin, 9.4 gm.; white blood cells, 12,600. Differential: Stabs, 2; segs, 52; lymphocytes, 37; monocytes, 8; eosinophils, 1. Urinalysis, negative.

C reactive protein, 3 plus.

January 14, 1955: Circulating eosinophils, 11 per cubic millimeter.
January 16, 1955: Circulating eosinophils, none per cubic millimeter.
January 17, 1955: Circulating eosinophils, 11 per cubic millimeter.

November 18, 1954: Urea nitrogen, 9.1.

January 19, 1955: Hematocrit, 36 vol. %; sedimentation rate, 13; glucose, 8:30 a.m., 140; total protein, 7.5; serum albumin, 4.3; serum globulin, 3.2; cholesterol, 142; cholesterol esters, 47.

Red blood cells, 3,550,000; hemoglobin, 10.4 gm.; white blood cells, 14,300. Differential: Segs, 74; lymphocytes, 23; monocytes, 3.

January 19, 1955: Circulating eosinophils, 33 per cubic millimeter.
Gamma globulin, 1.4 gm.

January 21, 1955: Circulating eosinophils, 22 per cubic millimeter.
January 22, 1955: Circulating eosinophils, 33 per cubic millimeter.
January 24, 1955: No circulating eosinophils found.
January 19, 1955: C reactive protein, 3 plus.
January 25, 1955: No circulating eosinophils.
January 12, 1955: Hemoagglutination test for rheumatoid arthritis, less than 1 to 14 (negative).
January 26, 1955: Circulating eosinophils, 11 per cubic millimeter.
January 27, 1955: Circulating eosinophils, 11 per cubic millimeter.

Summary of Necropsy Findings (by M. G. Bohrod, M.D.): The outstanding necropsy finding was very marked thickening of numerous arteries, both visceral and peripheral (figures 6 and 7). Aneurysmal dilatation was present in both brachial arteries (figure 8). Visceral involvement was found in almost every organ examined, but was especially marked in the heart, kidneys, spleen, liver, adrenals and

gastrointestinal tract. Large vessel involvement included the abdominal aorta, iliac arteries, femoral arteries almost to the popliteal and axillary, and brachial arteries almost to the elbow. In the arms and legs the transition from thick vessels (14 mm.) to the normal size (3 mm.) was rather abrupt. The large branches of the aorta, like the carotids, were moderately thickened; the smaller branches, like the intercostals, were relatively much more involved, starting abruptly at their origins.

Histologically, a variety of types of arteritis were seen, including necrotizing arteriolitis and arteritis and occasional giant cells, but by far the outstanding lesions were endarterial and muscular. The lumina of the vessels were tiny or, in some places (coronary, mesenteric), occluded by a recent blood clot. The enormously thickened walls were made up of proliferating fibroblasts, with relatively little lymphocytic or other inflammatory cellular infiltrates. There were scattered foci of necrosis in the proliferating fibroblastic tissue, sometimes quite large, but well defined rheumatoid granulomas were only rarely seen. The elastic tissue was markedly changed, destroyed, fragmented and, in places, piled up into masses.

The lungs were relatively free of lesions, although a very few could be found microscopically. Only a single focus of involvement was found in the cerebral

FIG. 8. *Case 7.* Aneurysmal dilatation of brachial artery.

vessels; one intrameningeal artery showed a plaque of endarteritic fibroblastic proliferation which encroached upon the lumen.

Secondary parenchymal changes were the result of the vascular narrowing of occlusion. In the heart there were numerous microscopic foci of necrosis, but there was also one large, grossly visible necrotic area in the myocardium (7 to 8 mm.). In the spleen there were several infarcts up to 15 mm. in diameter. The kidneys showed a "geographic" type of marking due to alternate areas of cyanotic and anemic tissue.

Case 8 (*Periarteritis Nodosa*). This 45 year old Negro male was admitted to the Rochester General Hospital October 25, 1954. He had first become ill in September, 1954, at which time he developed pain in the back of his neck associated with headaches. The pain spread and involved the arms and legs. At first it seemed to be limited to the joints, but later it was also felt in the muscular parts. In October, 1954, it became impossible for him to walk because the pain was generally worse and his legs were weak. He developed a slight cough, for which he took some "cold pills." His appetite decreased, and his feet began to swell about eight days

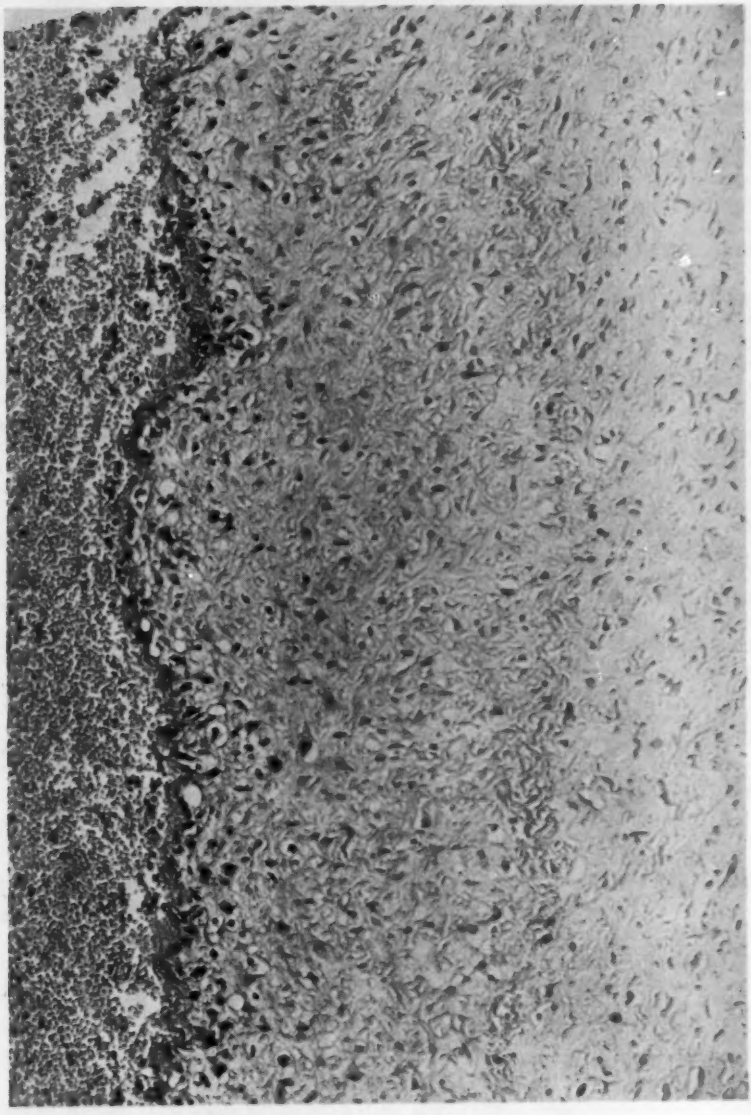

FIG. 9. *Case 7.* Lack of inflammatory reaction in iliac artery. The thickened wall was made up of proliferating fibroblasts.

before admission. Six days before admission he had a shaking chill, followed by a sensation of fever. He had lost 30 to 40 pounds since the onset of his illness.

Past History: The patient had had pneumonia twice prior to 1954. He had had gonorrhea and syphilis while in the Army in 1943, for which he was treated with injections. A spinal tap in 1953 was negative. The salient features brought out by the physical examination were as follows: Blood pressure, 160/120 mm. of Hg; temperature, 98° F.; pulse, 84; respirations, 14. He was unusually tender over the posterior aspect of the iliac crests. Edema was present in the feet. Marked muscular weakness was noted. The lymph nodes in the right groin were enlarged. Biopsy of one of these nodes showed benign hyperplasia and moderate fibrosis. After a week in the hospital he noticed tingling and numbness in his right leg and along the flexor surface of the fourth and fifth digits of the right hand. There was definite muscular weakness of the right leg and right hand.

On November 6, 1954, a left foot drop was present. A pinprick was not felt over the medial dorsal surface of the left foot and ankle. Vibratory sense was absent in the left ankle.

A biopsy of the right calf muscle showed "acute myositis and necrotizing vasculitis" consistent with either (1) dermatomyositis, or (2) periarteritis nodosa.

On November 12, 1954, cortisone therapy was started in the following daily dosage: first day, 600 mg.; second day, 500 mg.; third day, 400 mg.; fourth day, 200 mg.; fifth day and day after until November 22, 1954, 100 mg. daily. On the latter date the dose was again raised to 200 mg. daily.

On November 22, 1954, there was evidence of some improvement, as shown by the return of sensation on the dorsal lateral aspect of the foot and left shin.

On November 26, 1954, he complained of severe pain, swelling and tenderness of the right testicle, which began to recede two days later.

On November 30, 1954, he was able to get about with the aid of crutches for the first time. Pain in the legs and neck had almost disappeared, and the patient felt stronger.

On December 15, 1954, he was discharged on a maintenance dose of 100 mg. of cortisone daily, with supplementary potassium chloride. He was feeling much better, was having no pain and was able to get around with the aid of crutches. His blood pressure tended to rise. Attempts to lower the cortisone dosage were met by immediate aggravation of his symptoms. It was therefore decided to re-admit him for treatment with metacortandracin (Meticorten).

On admission on February 4, 1955, his blood pressure was 170/125 mm. of Hg. There was no edema; some right testicular atrophy was present, and the deep reflexes were hypoactive. The abdominal reflexes were present. The plantar reflexes were not elicited. The temperature was normal throughout this hospitalization.

Metacortandracin was started February 10, 1955, in a dosage of 30 mg. per day. Five days later this was decreased to 25 mg. per day, and at the end of another five days it was decreased to 20 mg. per day. On February 15, 1955, there was weakness of the flexors and extensors of the right arm and left leg, and absence of ankle jerks and decreased knee jerks. There was diminished sensation to pinprick, vibration and temperature in the right forearm and the entire left leg. He was discharged February 16, 1955, to be followed in the Out Patient Department.

Case 9 (Periarteritis Nodosa). A clinical diagnosis of periarteritis nodosa was made on this 39 year old white male on the following findings:

1. Renal involvement, as evidenced by albuminuria and an azotemia of 43 mg.%.
2. Joint symptoms and an increased sedimentation rate since March, 1948.
3. The following radiographic findings on February 23, 1955: "The presence of pleural pericardial adhesions and pleural thickening suggesting the presence of

polyserositis. In addition, there was a mottled infiltration at the bases of both lungs consistent with a chronic inflammatory process."

4. Electrocardiographic findings on February 5, 1955: regular sinus rhythm of 90; PR interval, 0.15 second; qRs, 0.08 second; inversion of T waves in T_1 and V_4, and depression of ST segment in V_6.

5. The suggestion of coronary artery involvement by the development of anginal symptoms.

6. Low grade fever and weakness.

7. The ruling out of disseminated lupus erythematosus by absence of L.E. cells in the blood on February 22, 1955, February 25, 1955, and March 3, 1955.

The patient was placed on metacortandracin on March 11, 1955, in the dosage noted under "Method of Study." Within a period of two days the temperature returned to normal and the anginal symptoms disappeared, and after another three day period all râles in the lungs had disappeared. His asthmatic breathing also disappeared, and this clinical improvement has been maintained to date on 20 mg. of metacortandracin daily.

The clinical pattern of multiple system involvement in the absence of the finding of L.E. cells favors a diagnosis of periarteritis nodosa.

Summary and Conclusions

Nine patients, six with disseminated lupus erythematosus and three with periarteritis nodosa, have been treated with metacortandracin. One patient with periarteritis nodosa died while under treatment. The autopsy showed extensive arterial involvement, both visceral and peripheral. The most remarkable feature in the histologic study was the lack of inflammatory process noted in the diseased arteries. The inference from these studies is that, if this patient had been treated in the early phase of the disease, the outcome would have been more favorable. The other two cases of periarteritis nodosa have been converted from very ill people to a status of employability.

All six patients with disseminated lupus erythematosus had previously been treated with either cortisone or corticotropin. All have done much better with metacortandracin. However, in no instance have the L.E. cells disappeared either from the bone marrow or from the peripheral blood. The improvement in the blood picture in case 1 was marked. All six cases carry on their usual activities with little or no restriction. The capacity to tolerate a normal diet, without salt restriction or the addition of the large, gastric-disturbing doses of potassium required with the use of other steroids, is appreciated by these people.

The initial dose was 30 mg.—10 mg. every eight hours in all cases except case 7. The dose was decreased by 5 mg. every five days until the smallest amount required for maintenance was reached. It was usually 15 to 20 mg. per day.

All of these patients with the exception of case 5 (L.E.) have been observed under treatment for from 60 to 120 days. This is still a short time although the short-term treatment has been favorable, more time will have to elapse before a conclusive opinion can be reached as to long-term treatment of the collagen diseases with this new compound.

ACKNOWLEDGMENTS

The authors appreciate the courtesy of Fred W. Bush, M.D., Chief, Department of Pediatrics, the Rochester General Hospital, for allowing them to treat and observe case 7, and Milton G. Bohrod, M.D., for his coöperation in the pathologic study of the same case. Mr. Jack Beiter and his staff of the Medical Photography Department of the Rochester General Hospital were most coöperative in providing the medical photography of this article.

SUMMARIO IN INTERLINGUA

Sex patientes con disseminate lupus erythematose e tres con periarteritis nodose esseva tractate con prednisona (Meticorten). Le dose initial esseva 30 mg (10 mg cata octo horas) pro omne patientes, excepte un qui habeva solmente duo annos. In su caso le dosage usate variava ab 15 a 20 mg per die. Le doses esseva reducite per 5 mg omne cinque dies usque le minimo de mantenentia esseva attingite. Isto esseva generalmente inter 15 e 20 mg per die. Un patiente con periarteritis nodose moriva durante le tractamento. Le autopsia revelava un extensissime involvimento arterial, tanto visceral como etiam peripheric. Le plus remarcabile observation del studio histologic esseva le absentia de omne processo inflammatori in le arterias morbose. Le conclusion supportate per iste studios esseva que si iste patiente habeva essite tractate durante le prime stadios del morbo, le resultato haberea essite plus favorabile. Le altere duo patientes con periarteritis nodose ha cessate esser personas invalide; illes ha re-attingite un stato de empleabilitate.

Le sex patientes con disseminate lupus erythematose habeva recipite previe therapias a cortisona o corticotrophina. Pro omnes le effectos de prednisona ha essite multo melior. Nonobstante, nulle del casos monstra un disparition del cellulas de lupus erythematose ab o le medulla ossee o le sanguine peripheric. In un caso le melioration hematologic esseva marcate. Le conto leucocytic montava intra un periodo de 24 horas ab 1300 a un nivello normal. Omne le sex patientes exerce lor activitates usual con pauc o nulle restriction. Illes es grate de poter tolerar un dieta normal, sin restriction de sal e sin le addition del grande doses de kalium (con lor effecto de disturbationes gastric) que es un indispensabile adjuncto in le uso del altere steroides.

Omne le patientes del presente serie, excepte le un qui moriva, esseva observate sub tractamento durante periodos de inter 60 e 120 dies. Tal periodos es certo breve. Ben que le tractamento a breve durantia ha essite favorabile, plus longe periodos de tempore debe passar ante que nos pote formular un opinion conclusive in re le uso del nove composito in le tractamento a longe durantia del morbos collagenic.

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RHEUMATIC FEVER PNEUMONITIS: A CLINICAL AND PATHOLOGIC STUDY OF 35 CASES *

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Introduction

In acute rheumatic fever pulmonary changes sufficiently developed to require separation from other diseases were observed in 35 cases of rheumatic fever terminating fatally during an acute phase of the disease and studied at necropsy. The morbid pulmonary changes observed in the lungs were, however, not diagnostic of a specific entity. We have observed similar changes, in part or in varying degree, in other diseases, namely, interstitial pneumonitis of chemical irritation, polyarteritis, uremia, subacute bacterial endocarditis, and lung tissue adjoining pulmonary abscesses or infarctions. However, in acute rheumatic fever the incidence and the magnitude of the pulmonary change usually far exceed the otherwise similar alterations present in other diseases. It is for this reason that the pulmonary lesion might be referred to as rheumatic fever pneumonitis.

Paul [9] in 1928 noted that while frank bronchopneumonia may occur as an intercurrent infection in any stage of rheumatic fever, it was relatively uncommon. He observed histopathologic characteristics, in the cases studied at autopsy, sufficiently different from the usual type of secondary pneumonia to warrant a suspicion of the specificity of the change. Masson [6] in 1937 described an inflammatory reaction in the lungs of 13 patients with rheumatic fever, characterized by a peculiar collection of cellular tissue in the form of buds which filled the alveolar ducts and spaces. Neubuerger [8] in 1944 reviewed 63 autopsy cases of rheumatic fever, in which eight cases showed the distinctive microscopic changes described by Masson, and assigned the term "Masson body" to the lesion. Herbut [4] in 1945 made similar observations. Seldin [11] in 1947 reported similar studies, and emphasized the rarity of intercurrent pneumonias in a control series. Levy [5] and others have added to the literature on this subject and have supported the relationship of the pulmonary lesion to the general manifestations of rheumatic fever.

Rich [10] in 1943 pointed out that the pulmonary lesions of rheumatic fever and sulfonamide hypersensitivity pneumonitis had basic histologic similarities. He doubted the specificity of the lesion and reported its recognition in a variety of pulmonary diseases, such as organizing pneumonia, lung abscess, bronchiectasis, pulmonary tuberculosis, interstitial

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pneumonitis and periarteritis nodosa. Gregory [2] in 1946 reproduced similar lesions in serum-sensitized rabbits, and also noted the occurrence in non-rheumatic patients, particularly where sulfa hypersensitivity was present. He supported the view that the lesions of rheumatic fever are the results of hypersensitivity, and that the pulmonary lesions of rheumatic fever are a part of this syndrome.

The clinical course of rheumatic fever is significantly modified by the presence of concomitant pneumonitis. Griffith [3] in 1946 studied a large series of cases of rheumatic fever and found a significant incidence of rheumatic fever pneumonitis. The presence of the pulmonary complication was more frequent in the severe forms of rheumatic fever, although occasionally the pulmonary manifestations anteceded the clinical manifestation of polyarthritis and carditis.

Method

In our study, the available autopsy material of patients who died in an active phase of rheumatic fever was reviewed and instances of pneumonitis were analyzed. The files of the Milwaukee Children's Hospital, Milwaukee County Hospital, Veterans Administration Hospital, Wood, Wisconsin, and some private cases furnished the source of the material. The clinical records were studied, and a composite clinical-pathologic picture was evolved.

Clinical Data

The incidence of rheumatic fever pneumonitis in each institution contributing material paralleled the character of admissions and the general incidence of rheumatic fever.

Table 1

Incidence of Rheumatic Fever Pneumonitis

Male	17	White	31
Female	18	Colored	3
		Mexican	1
	35		35

Age Distribution

1–5 yrs.	5–10 yrs.	10–15 yrs.	15–20 yrs.	20–30 yrs.	30–40 yrs.	Over 40 yrs.	Total
6	9	12	1	3	2	2	35

Table 2

Relationship to Attacks of Rheumatic Fever

First attack of rheumatic fever	17	
Second attack of rheumatic fever	11	1 previous congestive failure (not adm. with heart failure)
Third or more	6	1 previous congestive failure (not adm. with heart failure)
Chorea	1	
Total	35	

TABLE 3

Duration of Fatal Illness

0 to 2 wks.	2 to 4 wks.	4 to 8 wks.	Over 8 wks.
15	8	7	5

The large number of deaths which occurred during the first attack of rheumatic fever when the disease was complicated by pneumonitis is striking. The rather short duration of the last illness, with most of the cases terminating fatally within one month after the onset of first symptoms, attests to the severity and seriousness of this complication of rheumatic fever. The history of congestive heart failure in only two of the cases prior to the onset of fatal pneumonitis indicates the acute nature of the change.

TABLE 4

Presenting Symptoms

Dyspnea and tachypnea	34	
Severe cough	22	
Chest pain	20	
Cyanosis (often late)	22	
Hemoptysis	12	
Fever 101°–106°	29	16 Remittent, 13 Intermittent
Fever under 101°	3	
No fever	3	
Arthralgia	11	
Gastrointestinal symptoms	8	
Congestive heart failure		
First episode	1	
Recurrent episode	3	
No congestive failure but history of previous congestive failure.	2	

The symptoms occurred early in the development of pneumonitis, and their severity was striking. Respiratory distress, cough, chest pain, cyanosis and hemoptysis were prominent and out of proportion to the general health status of the patient, the degree of cardiac involvement, and the systemic manifestations of rheumatic fever. The degree of fever was higher than is ordinarily encountered in uncomplicated rheumatic fever. The incidence of congestive heart failure was no greater than would be expected in this number of cases of primary rheumatic fever and recurrences.

TABLE 5

Physical Findings in the Lungs

Migratory consolidation and congestion	19	
Persistent congestion	7	
Persistent consolidation	3	
Pleural effusion	1	(3 cases on x-ray)
Normal findings	5	
Total	35	

Physical findings in the chest were often widespread but notably migratory, with frequent periods of complete clearing. The severity of symptoms was as a rule strikingly out of proportion to the presence or extent of the physical findings in the chest. Only four cases in this series presented

signs of congestive heart failure in which the pulmonary findings were quite outstanding in contrast to the clinical picture. Pleural effusion seen in three patients on x-ray examination was sufficient in only one instance to be discovered on physical examination.

TABLE 6

Physical Findings in the Heart

Evidence of Valvular Disease		Additional Abnormalities			
		Disturbance of Rhythm			Pericardial Friction rub
Lesion	Number	Auric. fibrillation	A. flutter	Gallop	
Mitral systolic murmur	15	1	2	2	5
Mitral systolic and diastolic murmur	11			2	4
Mitral systolic and diastolic with aortic systolic and diastolic murmurs	7	1		2	1
Aortic systolic and diastolic murmurs	1				
No murmurs	1				1
Totals	35	2	2	6	11

There was evidence of active rheumatic carditis in all cases. This is impressive, in view of the high incidence of first attacks of rheumatic fever in this series and the generally short duration of the illness. The degree of cardiac involvement, however, was less than would have been expected if the symptoms were to be attributed to the heart disease alone. The clinicians repeatedly noted at the bedside that the severity of the symptoms did not parallel the cardiac findings. Intercurrent pneumonia, subacute bacterial endocarditis, pulmonary infarctions, isolated myocarditis, salicylate intoxication and other complications were offered by the observers as possible explanation for this discrepancy.

TABLE 7

Routine Laboratory Studies

Procedure	Urinalysis		White Blood Count				Westergren Sedimentation Rate			Multiple Blood Cultures	
No. of Pts. examined	26		33				23			20	
Significant results	Albumin Trace to 2+	Normal	12,000 to 20,000	20,000 to 30,000	Over 30,000	Normal	15–40 mm.	40–100 mm.	Normal	Neg.	Pos.
	23	3	19	10	3	1	4	17	2	20	0

The laboratory findings were not remarkable in a series of acutely ill patients with rheumatic fever. The number of cases in which multiple blood cultures were taken (20 of 35) reveals the high degree of suspicion on the part of the physicians managing the clinical problem that they were dealing with something other than ordinary rheumatic fever.

TABLE 8

Electrocardiographic Changes

Sinus Tachycardia	Auricular Fibrillation	Auricular Flutter	First Degree Heart Block	St and T or T-wave Changes	Normal	Total Cases
4	1 1*	1 1†	2	3	2	15

* Including right bundle branch block.
† With first degree heart block and intraventricular conduction defect.

The electrocardiographic observations were not frequent enough in this series to warrant comment.

TABLE 9

X-Ray Changes

Nature of Parenchymal Changes	Cases
Stellar radiation from both hili with linear parenchymal densities, occasionally beaded along vascular markings, and with clear apical and basal areas (figure 1).	8
Diffuse parenchymal mottling, nodular stippling of miliary type, and occasional confluent areas of small nodular lesions. Apices and bases clear. Miliary calcifications in one instance (figure 2).	9
Diffuse clouding of both lung fields (figure 3).	2
Stellar radiation from both hili with unilateral massive consolidation, and pleural effusion in two instances, migrating areas of consolidation in the other two. Apices and bases clear (figure 4).	4
Massive bilateral consolidation, central in origin. Unilateral pleural effusion in one instance (figure 5).	4
No x-ray taken	8
Total	35

The character of the x-ray appearance suggests evolution from perivascular increase in density arising at the hilus, and often associated with beading along the bronchovascular markings, to small miliary nodular infiltration of the lung parenchyma and ultimately to confluence of lesions to form massive areas of consolidation. In no instance, however, were serial x-rays taken frequently enough to offer proof of this supposition.

While the appearance of the x-ray lesion is not pathognomonic, the basic patterns differ sufficiently from those observed in uncomplicated pulmonary congestion to warrant a serious suspicion of the presence of rheumatic fever

pneumonitis. Seldin [11] et al. called attention to the infrequency of intercurrent pulmonary infection during the course of active rheumatic fever, and this would further suggest that pulmonary x-ray changes in acute rheumatic fever may represent a direct and integral part of the disease itself.

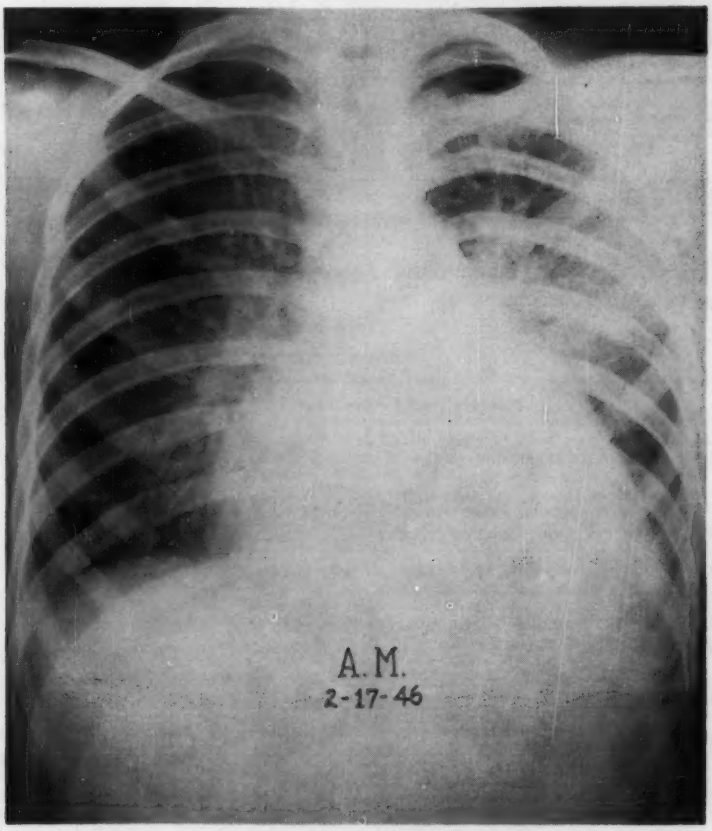

FIG. 1. Stellar radiation from both hili with linear parenchymal densities, occasionally beaded along vascular markings, and with clear apical and basal areas.

PATHOLOGIC FEATURES

In many instances the appearance and gross characteristics of the lungs are highly suggestive (figure 6). The lungs are several-fold increased in weight, and this depends principally upon the amount of hemorrhage and edema present. The lung tissue is rubbery firm in consistency, but this may vary in different areas depending upon the amount of hemorrhage, "organization" and degree of aeration. Usually all cut surfaces are uni-

formly flat, have sharp stiff edges, and appear finely granular and mimic closely the alveolar fibrin plug granularity of lobar pneumonia. Intervening areas of aerated lung generally have the "pigskin" appearance of vesicular emphysema. The color of such lungs ranges from bright red through shades of bluish red and rusty brown. These variations are correlated with the many episodes of hemorrhage that occur at intervals of time. No

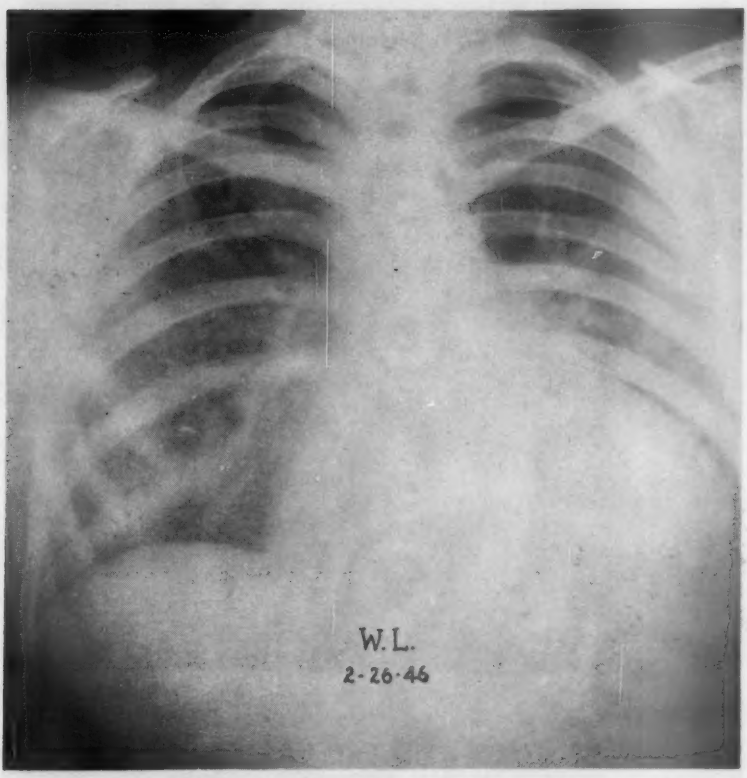

FIG. 2. Diffuse parenchymal mottling, nodular stippling of miliary type, and occasional confluent areas of small nodular lesions. Apices and bases clear. Miliary calcifications in one instance.

constant distribution of the changes has been observed, although the hilar and the peripheral areas are generally darker than the midfield zones. The peripheral areas are frequently fan-shaped in appearance, particularly when the zone of hemorrhage is fresh.

Pathologic histology may be summarized under the following headings:

Alveolar Hemorrhages (figure 7): This finding, present in all cases, varied according to the time of the occurrence and magnitude of involve-

ment. All specimens had evidence of old hemorrhage, with presence of pigment-laden macrophages accompanied by some fibrin and in certain areas occasional fibroblasts of organization. Other areas were those of fresh hemorrhage, with intact erythrocytes accompanied by abundant fibrin-poor edema fluid. In these areas the alveolar lining cells were variably increased in number and the alveolar walls showed frequent zones of fibrinoid necrosis.

Alveolar Wall Necrosis (figure 8): In various degrees this finding is also present in all cases and is ordinarily accompanied by acute hemorrhage

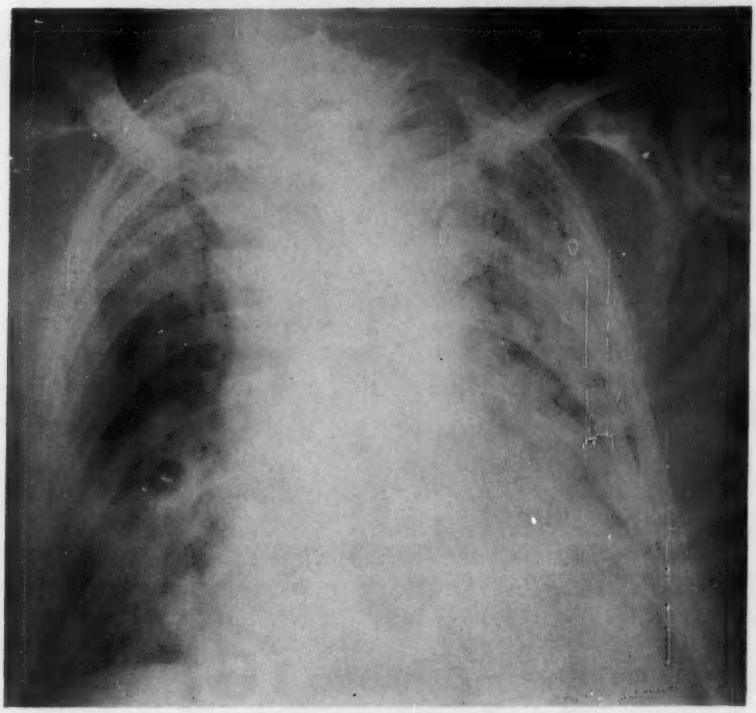

FIG. 3. Diffuse clouding of both lung fields.

in such areas. The eosinophilic necrosis can be seen originating in the basement membrane of the alveolar septum in which swelling and fragmentation are prominent. This appears to be rapidly followed by agglutination of red cells and thrombosis in the alveolar capillaries. Eventually the entire septal wall is converted to a granular, highly eosinophilic mass in which numerous nuclear particles of debris are seen (necrotizing alveolitis). In some areas as much as one-half of the alveolar outline may

be completely necrotic and fractured. Such necrosis is particularly apt to occur near the atrial ducts, and to produce small buds of alveolar septal tissue capped by fibrin exudate. In these areas edema fluid is present and hyaline membranes are frequent.

Hyaline Membrane (figure 9): Lining the atrial ducts are wide fuzzy or sharply outlined bands of eosinophilic amorphous material that extends

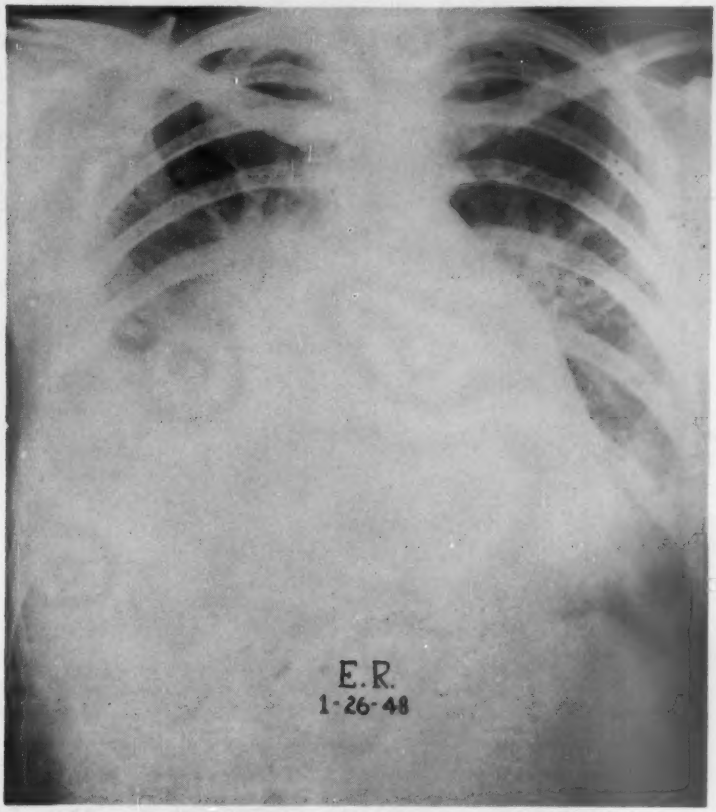

FIG. 4. Stellar radiation from both hili with unilateral massive consolidation, and pleural effusion in two instances, migrating areas of consolidation in the other two. Apices and bases clear.

into the alveolar divisions for variable distances. These membranes are accompanied by considerable alveolar lining cell proliferation, hemorrhage, and fibrinoid change of the alveolar septa. This pattern, however, is quite spotty in development and is seen more commonly in the lower lobes in the dependent portions and particularly in the subpleural areas. The exact

mechanism of this hyaline membrane production is not known, but some physicochemical change of the alveolar fluid apparently takes place as the fluid is gurgled through the atrial ducts during respiration. It appears to be an albuminous material that may represent "inspissated" protein of pulmonary edema.

Alveolar Lining Cell Proliferation (figure 10): This change is commonly found around the periphery of the zones showing acute fibrinoid necrosis. It is characterized by a highly cellular alveolar septum in which there are numerous nucleated cells and young fibroblasts. The lining cells may be

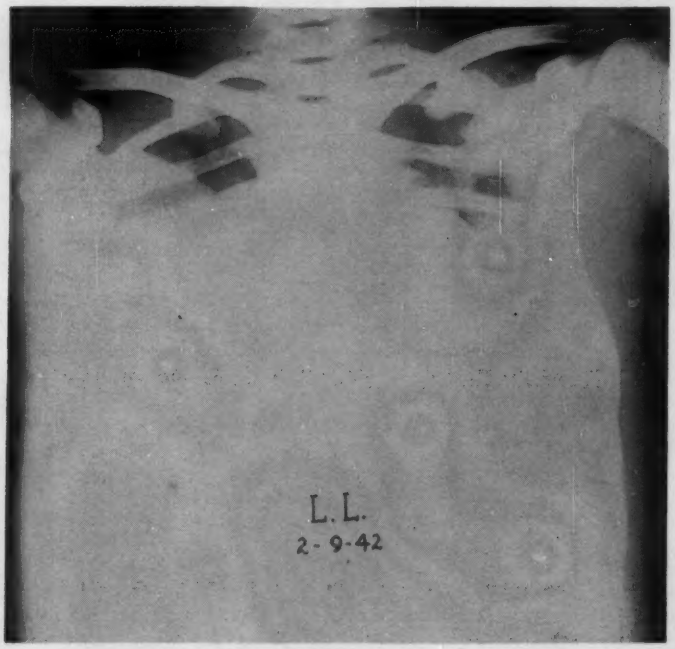

FIG. 5. Massive bilateral consolidation, central in origin. Unilateral pleural effusion in one instance.

a part of an alveolar wall mass or may be a separate collection of large hyperplastic mononuclear cells lying free in the alveolar space. In the instances where the alveolar wall is thickened by such cell proliferation the cells do not have any consistent orientation and have a uniform eosinophilic cytoplasm, features which do not suggest an Aschoff nodule.

Organization Bodies (figure 11): In many instances the fibrinoid necrosis of the alveolar wall produces a nodule of eosinophilic granular material covered by alveolar lining cells which proliferate and infiltrate into the fibrin mass. In other instances it appears that fibrin and necrotic sub-

stance attached to or lying free in the alveolar space are accompanied by alveolar lining cell proliferation and infiltration, with early conversion of such cells to fibroblasts. These areas then have a spindle shape and have polarized nuclei in the mass. Again, the arrangement and type of the cells are not particularly suggestive of the Aschoff nodule as seen in the myocardium in its typical form. The organizing masses of the alveolar wall are referred to as Masson bodies.

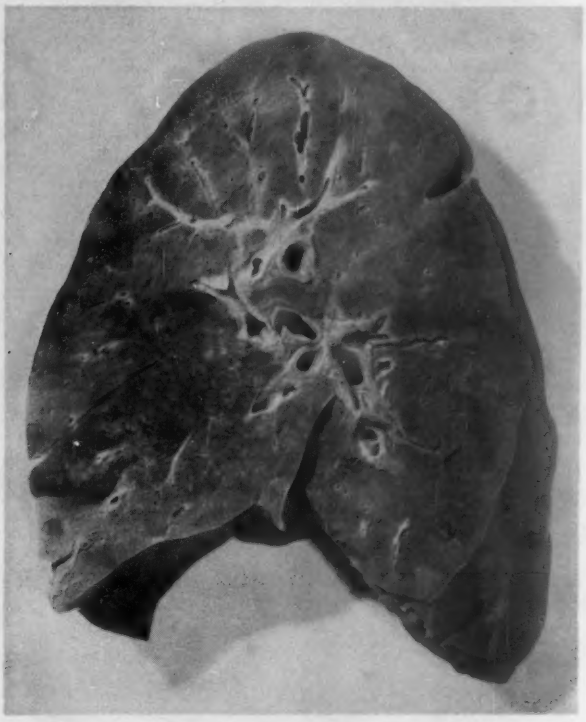

FIG. 6. Lung showing vesicular emphysema and mottled coloration due to congestion and hemorrhages.

Bronchiolar Changes (figure 12): The bronchiolar changes consist principally of spotty or uniform eosinophilic granular necrosis of the lamina propria. In a number of instances as much as one-half of the circumference was completely altered, making identification rather difficult. Eventually the muscular coat also takes part in the process. The lining epithelial cells are frequently desquamated, and only occasional tufts of respiratory epithelium remain. This particular change has not been given proper significance in previous reports. We have not been able to correlate this particular change with the hyaline membrane of the respiratory ducts.

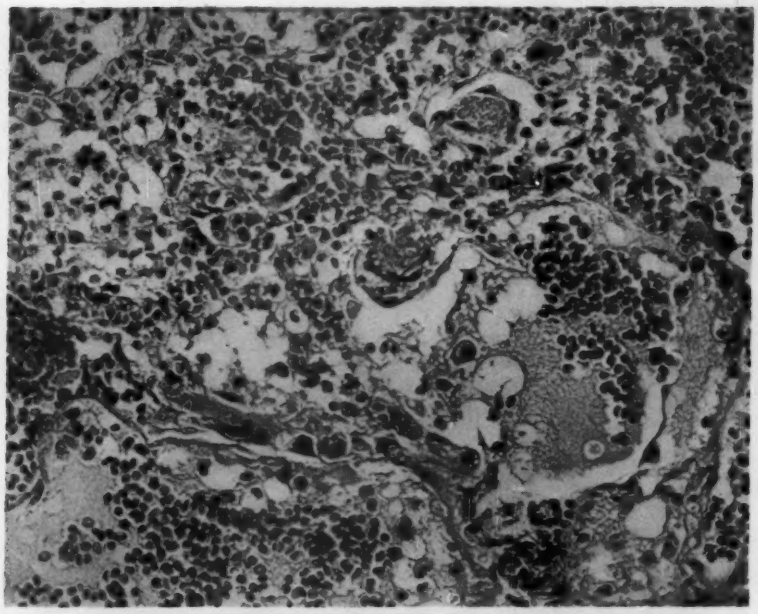

FIG. 7. Numerous red blood cells and edema fluid in the alveoli. Two fibrin buds are seen above midfield.

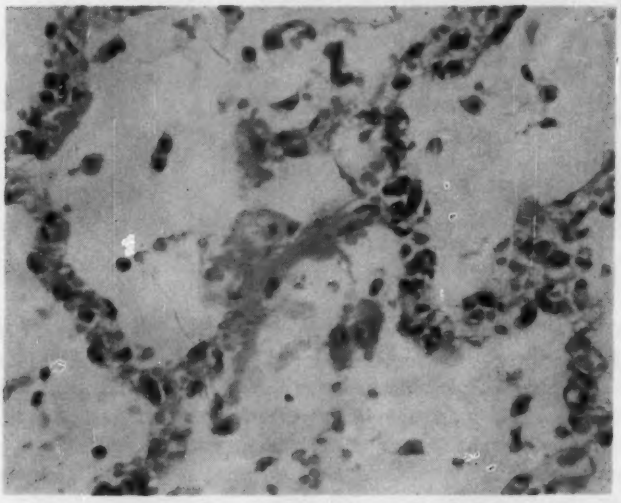

FIG. 8. In the center of the photomicrograph there is fibrinoid necrosis of the entire alveolar wall associated with fibrin on the surface and two lining alveolar cells adjacent to this altered alveolar wall. Other areas show marked congestion.

Blood Vessels (figure 13): Pulmonary blood vessels as well as other vessels of the body also show changes, beginning apparently as eosinophilic granular necrosis of the elastic lamina and intima. This may involve the entire circumference or only a segment of the vessel, and is followed by proliferation of fibroblasts and mononuclear cells which may produce complete occlusion of the necrotic vessel. Generally in the early phases there is little or no reaction around the periphery of the necrotic vessel, but eventually inflammatory cells are found in the adventitia, and these are principally lymphocytes, mononuclear cells, and polymorphonuclear cells.

The intima-elastica necrosis in the stage of repair shows intimal fibroblastic proliferation that produces marked narrowing of the lumen. In some

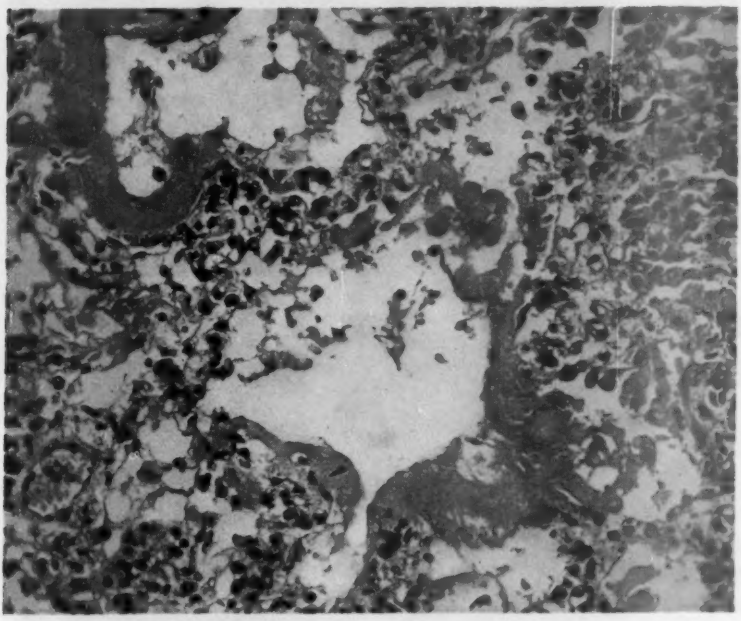

FIG. 9. Well developed hyaline membranes in the atrial ducts accompanied by interstitial inflammatory reaction.

vessels more than half of the entire vessel wall thickness is composed of the spongy young connective tissue of the intima. Complete obliterative endarteritis is occasionally seen.

DIFFERENTIAL DIAGNOSIS

In all of our cases the diagnosis of rheumatic pneumonitis was first made at the autopsy examination. While in no instance was the diagnosis made ante mortem, it was suspected on two occasions. Significantly, in almost all instances the attending clinician was aware of the unusual course of active

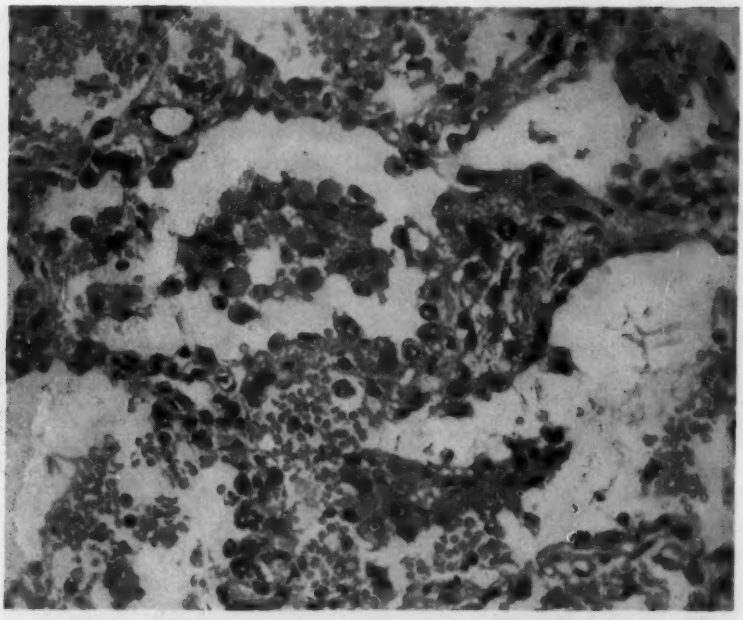

FIG. 10. Marked thickening of the alveolar wall associated with an attached mass of proliferating lining cells. Histiocytes and desquamated lining cells lie free in the alveolar spaces accompanied by red blood cells.

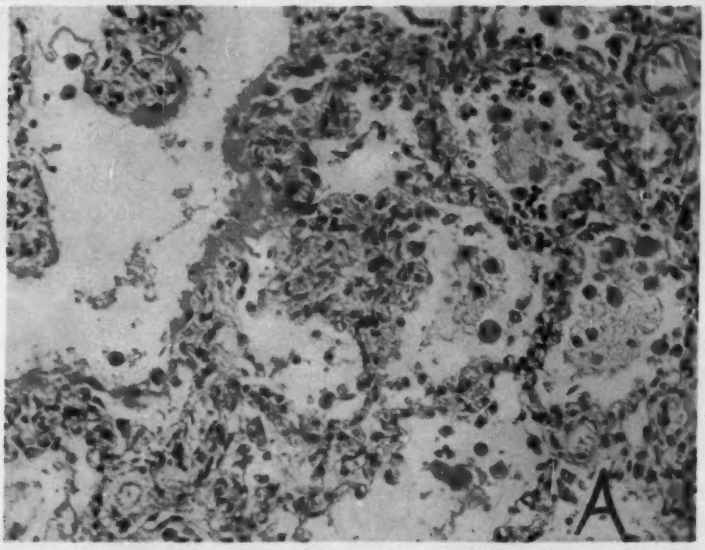

FIG. 11. Organizing Bodies: *A*. In the center is an expanded alveolar wall showing fibrinoid necrosis but also a generous proliferation of histiocytes.

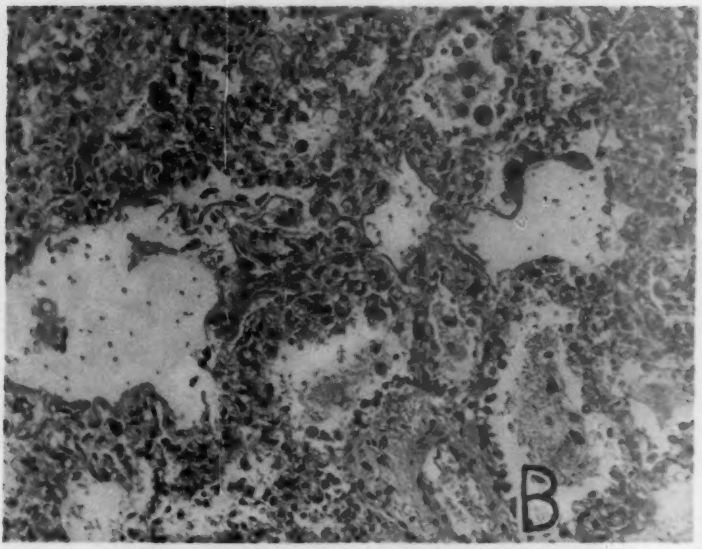

FIG. 11 *B*. Similar reaction, later in development, shows orientation of histiocytes and fibroblasts. This development is taking place in the wall of an atrial duct.

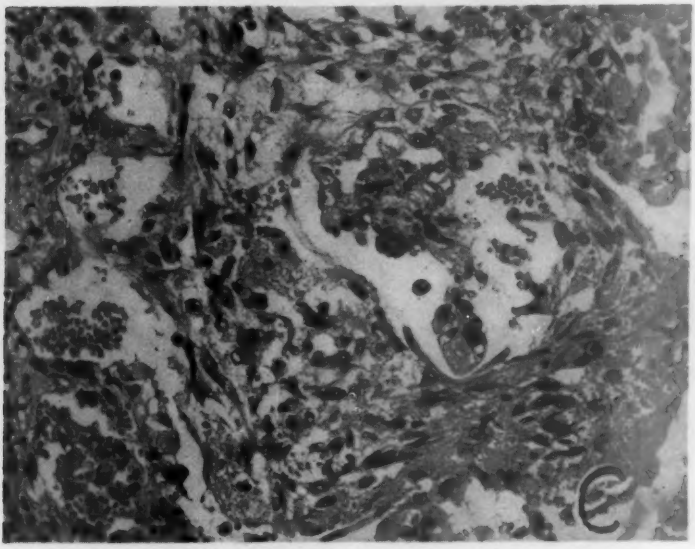

FIG. 11 *C*. Alveolar exudate organization with polarization of the nuclei in the right lower portion of the photomicrograph.

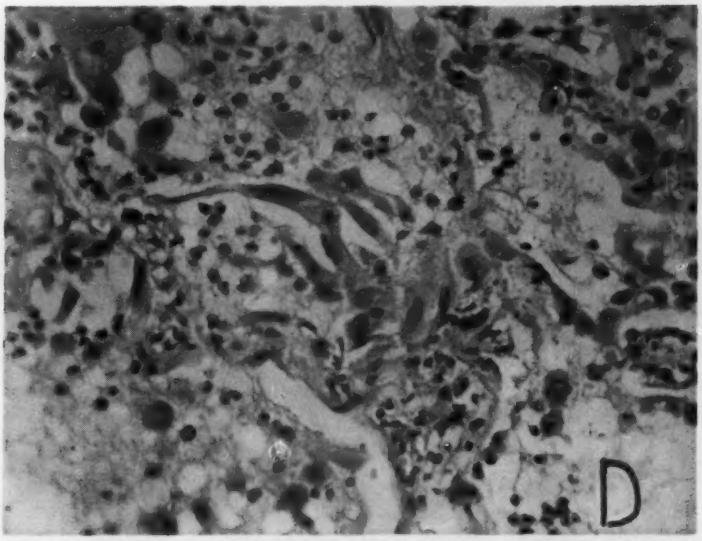

FIG. 11 *D*. Interstitial cellular proliferation with large hyperchromatic histiocytes vaguely suggesting Aschoff's nodule.

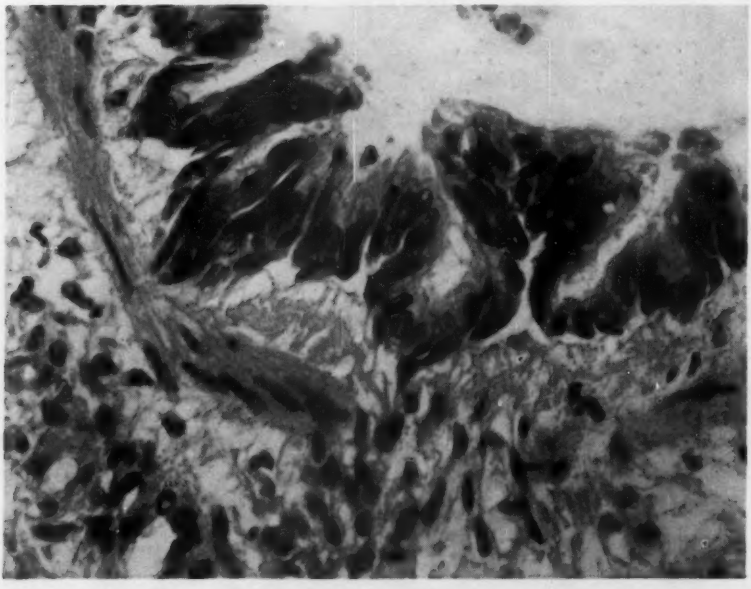

FIG. 12. Bronchiolar wall showing marked swelling, fragmentation and development of various sized vacuoles in the lamina propria undergoing fibrinoid necrosis.

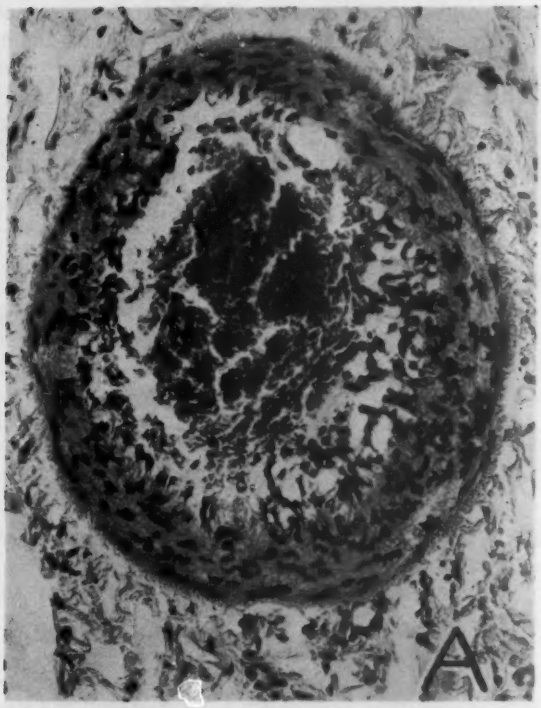

FIG. 13. Arteritis: *A*. Early fibrinoid necrosis and inflammatory reaction of pulmonary arteriole.

rheumatic fever, and many complications of the disease were postulated as possible explanations for the unexpected events. A better appreciation of the clinical manifestations of rheumatic pneumonitis and a higher index of suspicion of the presence of this complication could have yielded some correct antemortem diagnoses. The working diagnoses noted by the clinician in attendance are of interest, and reflect the scope of the differential diagnosis:

TABLE 10

Working Diagnoses

Heart failure	8
Heart failure and pneumonia	3
Subacute bacterial endocarditis	3
Subacute bacterial endocarditis and heart failure	4
Subacute bacterial endocarditis and pneumonia	7
Pneumonia	3
Pulmonary infarction	2
Isolated myocarditis	1
Salicylate intoxication	1
Uncomplicated acute rheumatic fever	3
Total	35

The presence of unusually severe respiratory distress, not associated with cardiac and peripheral features of congestive heart failure and nonresponsive to supportive management, should arouse the suspicion of the presence of rheumatic pneumonitis. Severe cough, chest pain, cyanosis and hemoptysis, particularly if severe and prolonged, warrant particular appraisal, as does high, prolonged fever (in the absence of positive blood cultures) which does not respond to salicylate therapy. The lack of history of previous attacks of rheumatic fever need not distract from the diagnosis.

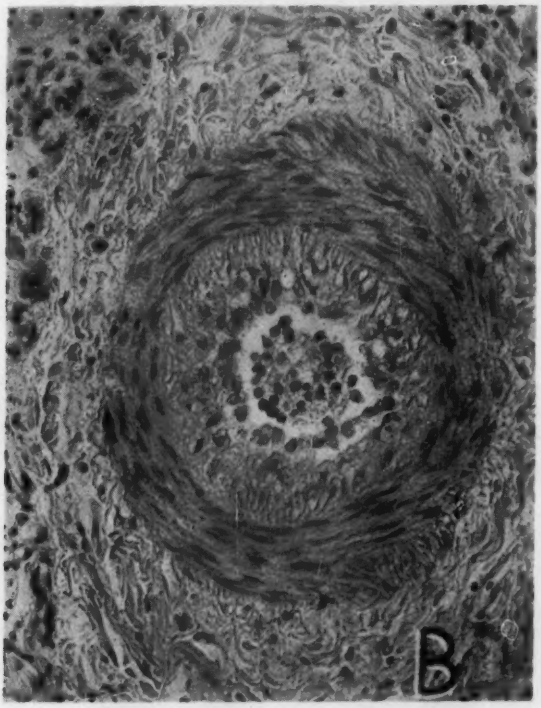

FIG. 13 *B*. Later stage with intimal proliferation.

Migratory physical signs of pulmonary congestion and consolidation in the absence of pleural effusion and other evidences of congestive heart failure are helpful. Clinical evidence of carditis appears to be constant when rheumatic pneumonitis is present. Routine laboratory studies and the electrocardiographic findings reflect the basic pattern of rheumatic fever and appear to be of no special value in the differential diagnosis. The demonstration of suggestive x-ray changes, coupled with the clinical observations, should be sufficient evidence to warrant the diagnosis of rheumatic pneumonitis.

Treatment

The treatment, in our series, was based upon the consideration of the working diagnosis. This included the usual salicylate management of acute rheumatic fever; the supportive measures for suspected congestive heart failure, such as oxygen, digitalis, salt restriction and mercurial diuretics; and antibiotic therapy where subacute bacterial endocarditis was suspected. The unfavorable progression of the clinical course was not altered by this management. The failure of oxygen to relieve the respiratory distress was notable.

In one case, where the diagnosis of rheumatic pneumonitis was suspected, intravenous ACTH was employed. In this instance the fever subsided, the sedimentation rate became normal, the heart became smaller and signs of carditis seemed to regress, but the respiratory distress increased, and x-ray evidence of rheumatic pneumonitis was particularly extensive. The pathologic changes were more strikingly developed in this case than in the remaining cases in our series that had not received ACTH therapy. The severity of the case probably rendered ACTH ineffective. Chancey [14] has had contrary experience.

No suggestion as to effective clinical management of rheumatic fever pneumonitis can be derived from our study. The antemortem recognition of this complication of rheumatic fever is the basic prerequisite for evolution of successful therapy.

Summary and Conclusions

1. Autopsy material from patients dying of rheumatic fever at the Milwaukee Children's Hospital, the Milwaukee County Hospital and the Veterans Administration Hospital and some private patients was studied. Thirty-five instances of rheumatic fever pneumonitis were discovered, and the pathologic material was reviewed. The clinical aspects of these cases were studied in retrospect.

2. The diagnosis of rheumatic fever pneumonitis is rarely made ante mortem. The seriousness of this complication of rheumatic fever warrants clinical interest directed toward more successful management. This is predicated on more frequent recognition of rheumatic fever pneumonitis during the acute phase of the disease.

3. Clinical diagnosis of rheumatic fever pneumonitis is warranted when there is:

A. Disproportionate respiratory distress with severe cough, chest pain, cyanosis and hemoptysis not relieved by oxygen and the customary supportive measures.

B. Evidence of carditis, but not of sufficient severity to explain the pulmonary findings, in the presence of prolonged high fever and negative blood cultures which do not respond to salicylates.

C. Chest x-ray finding of increased perivascular markings arising at the hilus and progressing to nodulation, confluence and massive consolidation with relatively clear apices and bases.

4. Gross pathologic changes are: rubbery consistency, various dark hues of focal hemorrhages, fine granularity and spotty vesicular emphysema.

5. Histologic changes are: alveolar hemorrhages, necrotizing alveolitis, hyaline membranes, alveolar lining cell proliferation, organization of exudate, fibrinoid necrosis of bronchiolar lamina propria and arteritis.

ACKNOWLEDGMENT

We are indebted to Dr. G. Ritchie and the Milwaukee Children's Hospital, Dr. J. M. Lubitz and the Veterans Administration Hospital, Wood, Wisconsin, and Dr. W. A. D. Anderson for the opportunity to study their cases.

SUMMARIO IN INTERLINGUA

In 35 casos de febre rheumatic a termination mortal in un phase acute del morbo, alterationes pulmonar esseva observate in formas sufficientemente disveloppate pro requirer lor separation ab altere morbos. Le alterationes esseva studiate necropticamente.

Le grossier alterationes histologic esseva hemorrhagias alveolar, alveolitis necrotisante, membranas hyalin, proliferation cellular del revestimento alveolar, organisation de exsudato, necrosis fibrinoide de bronchiolar lamina proprie, e arteritis.

Le diagnose de pneumonitis a febre rheumatic es rarmente facite ante morte. Le serietate de iste complication de febre rheumatic merita nostre interesse clinic, specialmente con le objectivo de disveloppar un plus efficace manipulation. Isto depende del plus frequente recognition de pneumonitis a febre rheumatic durante le phase acute del morbo.

Le diagnose de pneumonitis a febre rheumatic es justificate in le presentia de (1) disproportionate molestia respiratori con formas sever de tusse, dolor thoracic, e cyanosis e hemoptysis non subjicibile per oxygeno e le currente mesuras supportative; (2) signos de carditis, non sufficientemente sever pro explicar le constatationes pulmonar, in association con prolongate e alte febre e negative culturas sanguinee que non responde a salicylatos; e (3) constatationes roentgenologic de augmentate marcationes perivascular que prende lor origine al hilo e que progrede a nodulation, confluentia, e consolidation massive, durante que apices e bases remane relativemente clar.

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TOXEMIA OF PREGNANCY AS SEEN BY AN INTERNIST: AN ANALYSIS OF 1,081 PATIENTS * †

By FRANK A. FINNERTY, JR., M.D.,‡ *Washington, D. C.*

IN July, 1952, in conjunction with the Obstetric Department, a toxemia clinic was instituted at the District of Columbia General Hospital. A previous report,[1] analyzing the first 303 patients, suggested:

1. Differentiation between toxemia of pregnancy and hypertensive vascular disease was apparent by examination of the retina. Regardless of age, blood pressure level, or degree of edema or albuminuria, if a generalized retinal sheen was present (a wet, glistening appearance of the entire retinae), and the retinal arteries were normal, true toxemia existed. If no retinal sheen was present but hypertensive retinopathy was seen, hypertensive vascular disease existed. If both a sheen and hypertensive retinopathy existed, toxemia was superimposed on hypertension. Finally, if the ophthalmoscopic examination was normal and the arterial blood pressure found to be elevated, early hypertension existed.

2. It was seen that, although 95% of the patients referred to the clinic were originally diagnosed as toxemia by the obstetricians, only 14% had toxemia by our criteria.

3. It was suggested that vascular damage, as evidenced by retinal changes, followed toxemia in some patients. These retinal changes were related to the duration of the toxemia rather than to its severity. Since a greater experience has changed some of our ideas regarding classification, and since more refinements have been added to the concept of retinal sheen (particularly through the aid of fundus photography), it seemed worthwhile to report our further observations on these patients.

To date, 1,081 patients have been seen, some of whom have been followed for three years. The diagnoses for the 1,081 are seen in table 1, and include: hypertensive vascular disease, 666; hypertensive vascular disease plus toxemia, 90; postpartum hypertension, 72; true toxemia, 154; pyelonephritis, 56; edema without disease, 38; unrelated cardiac disease, five.

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Methods

Patients were seen weekly from the first sign or symptom of toxemia until term, or until hospitalization was advised. Since true toxemia is most common in the young primigravid, we followed all young primigravid patients (less than 16 years old) at weekly intervals after their first prenatal visit. Post partum, the patient was seen at three weeks, six weeks, three months and six months. From this point the patient was seen twice yearly, or until pregnant again.

Besides the usual obstetric examination, including weekly blood pressure determinations, a complete urinalysis was done at each visit. If albuminuria was discovered, a glitter cell stain and urine cultures were obtained. An ophthalmoscopic examination with the pupils dilated was performed at each visit. Serial fundus pictures of representative patients were taken with a Bausch and Lomb fundus camera. When pictures were to be taken, optimal dilatation of the pupils was afforded by instilling a

Table 1

Diagnoses in 1,081 Patients

Hypertensive vascular disease	666 patients
Hypertensive vascular disease plus toxemia	90 patients
Postpartum hypertension	72 patients
Pure toxemia	154 patients
Pyelonephritis	56 patients
Edema without disease	38 patients
Unrelated heart and kidney disease	5 patients
Total	1,081 patients

drop of 5% homatropine into each eye three times at five-minute intervals. (Without optimal dilatation, the resulting fundus pictures were worthless.)

Hypertensive Vascular Disease

Six hundred sixty-six patients were in this group. Ophthalmoscopically, this group can be divided into hypertensive disease with normal fundi (144) and hypertensive disease with abnormal fundi (522) (table 2). This latter group with abnormal fundi can be subdivided into those patients who remained hypertensive during their pregnancy (296), those whose blood pressure went down during pregnancy (196), and those with normal blood pressure, pregnant or not pregnant, and no other evidence of vascular disease (30).

In all patients, peripheral edema was absent, or was at the most 1 plus; periorbital edema was absent. Albuminuria was absent or was 1 plus.

The only abnormality in those patients who showed an elevated blood pressure with normal fundi was a persistent elevated blood pressure reading above 140/90 mm. Hg. The highest readings of arterial pressure consistently occurred either in the immediate postpartum period or some time

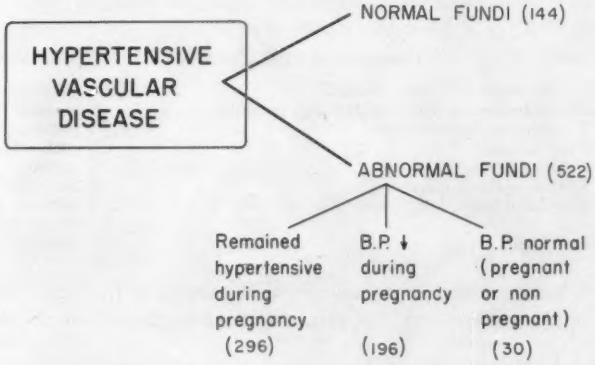
during the first two months postpartum, and not at delivery, as might have been expected.

In the group showing abnormal fundi, 360 showed grade 1 hypertensive changes (increased light striping and tortuosity), 156 showed grade 2 hypertensive changes (more pronounced grade 1 changes plus arteriovenous nicking), and six showed grade 3 changes (hemorrhages and/or exudates).

Two hundred ninety-six patients remained hypertensive during their pregnancy. Thirty per cent of this group had a history of "toxemia" with previous pregnancies. Since results of the examination of the optic fundi were not recorded during those earlier pregnancies, one cannot accurately state whether hypertension was present at that time. The highest blood pressure was in the last week of pregnancy, particularly at delivery and immediately post partum.

TABLE 2

Ophthalmoscopic Findings in 666 Patients


HYPERTENSIVE VASCULAR DISEASE
NORMAL FUNDI (144)
ABNORMAL FUNDI (522)
Remained hypertensive during pregnancy (296)
B.P. ↓ during pregnancy (196)
B.P. normal (pregnant or non pregnant) (30)

One hundred ninety-six of the hypertensive patients or approximately one third became normotensive or even hypotensive during pregnancy. All of these patients had known of hypertension in the nonpregnant state for at least one year, with an average blood pressure reading of 160/100 mm. Hg. When they were seen in the clinic during the first trimester of pregnancy, the arterial pressure was in the range of 100/60 mm. Hg, where it remained throughout pregnancy. The fundi showed grade 1 or grade 2 hypertensive changes. Immediately after delivery the patient would again become hypertensive, and the blood pressure would remain elevated until the next pregnancy. Of interest was the fact that the highest blood pressure readings in this group of patients would consistently be seen during the first two months post partum, particularly at six weeks post partum. By three to three and one-half months post partum the arterial pressure would usually return to its usual nonpregnant hypertensive level (figure 1).

There was still another group of patients with abnormal fundi whose blood pressures were in the normal range in the pregnant and nonpregnant state. This group was referred to the clinic by the obstetricians because of age only, *not* because of any obstetric or medical abnormality. These patients were all *under 17 years of age.* There was no history of hypertension, kidney disease or diabetes. Clinically and ophthalmoscopically, these patients resembled the group with hypertensive vascular disease with the blood pressure down during pregnancy, except for the fact that the blood pressure did not become elevated post partum. Examination of the optic fundi showed grade 1 changes (19 patients) or grade 2 changes (11 patients).

Comment

Except perhaps for their age, the group of hypertensive patients with normal fundi differs in no way from the large number of nonpregnant hyper-

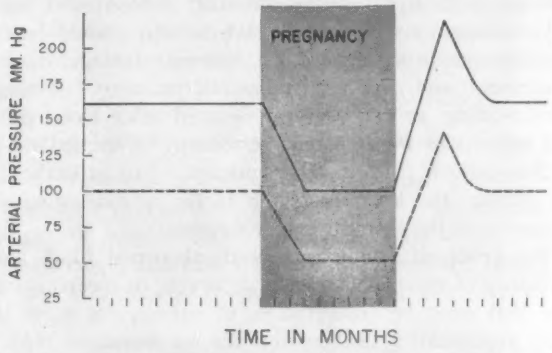


Fig. 1. Thirty-month chart of arterial pressure of E. C., a 26 year old hypertensive female patient. Note that the arterial pressure is highest during the first two postpartum months.

tensive patients seen routinely by the internist. The symptoms, if any, are related to anxiety and not to the arterial pressure. These are patients without evidence of vascular disease, except for the high blood pressure reading. This state, therefore, might better be called "a high blood pressure reading" than hypertensive vascular disease. As with the nonpregnant patient, there is no relation between the severity of the disease and the blood pressure reading. These patients with normal fundi present no problem medically or obstetrically. They respond well to oral Rauwolfia therapy (or mild sedation), and their pregnancy is in no way affected by the high blood pressure reading.

The overwhelming Negro population in our clinic (all except 19 were Negro patients) may explain, in part at least, the prominence of hypertension in this group, since hypertension is known to develop earlier in the Negro.[2] Without examination of the retina, however, many of these pa-

tients, particularly the group under 20 years of age, would be classified as having toxemia, and the severity of the toxemia judged by the height of the arterial pressure.

On the other hand, failure to examine the retina in the group of hypertensive patients whose blood pressure went down during pregnancy would account for a diagnosis of "normal pregnancy." Recognition of the abnormal fundi in this group forewarns the physician of the possible postpartum rise in blood pressure, which might or might not be significant. Though described by Dieckmann [3] and Teel,[4] the frequency of this phenomenon has not been appreciated. In our experience, the arterial pressure in hypertensive pregnant patients increases in one third, remains unchanged in one third and decreases in one third.

The finding of definite hypertensive changes and the absence of a retinal sheen (to be discussed below) in a pregnant patient with an elevated arterial pressure are reassuring to the physician. These patients are not toxemic—they are patients with hypertensive vascular disease who happen to be pregnant. The indications for hypotensive therapy should be the same as though the patient were nonpregnant, i.e., vascular damage, cerebral, cardiac or renal impairment, and/or a rising diastolic pressure. A single elevated blood pressure reading, or even several elevated office blood pressure readings, are not indications for hypotensive therapy or immediate hospitalization, nor do they indicate toxemia of pregnancy. Just as in the nonpregnant hypertensive patient, the least important factor in evaluating the severity of the hypertension is the blood pressure number.

Finally, the group of young girls with abnormal fundi and no other evidence or history of vascular disease is deserving of special comment. The first question that must be answered is, of course, are these blood vessel findings really abnormal? The possibilities are threefold: (1) these findings may be a variant of normal; (2) they may represent congenital tortuosity, or (3) they may indeed be abnormal.

That these findings (documented by funduscopic pictures) may be a variant of normal cannot be accepted under the criteria set forth by Wagener and Keith.[18] Thickening of the walls of the arteries, with increased intensity of the light stripe and tortuosity, is the least that has been seen in these patients. In five patients, arteriovenous nicking (grade 2 changes) has been evident. Everyone should readily admit that the finding of arteriovenous nicking is abnormal. Objections have been raised, however, that increase of the light stripe and tortuosity may not be abnormal, and it has been stated that without arteriovenous nicking one cannot say that the fundus is abnormal. If this statement is accepted, then an entirely new classification of ophthalmoscopic changes in hypertension is needed, for this deletes the so-called grade 1 changes.

Though congenital tortuosity of the retinal vessels may resemble the tortuosity due to vascular disease, there are several important differences.

In congenital tortuosity, the tortuosity is the only abnormality. The caliber of the vessels is normal; there is no thickening of the vessel walls or increase in arterial striping. The caliber of the tortuous vessels in our patients was abnormal. They were thicker than normal, with an increase in arterial reflex stripe. When the retinal vessels showed only tortuosity, they were not designated as abnormal.

A straightforward statement that these retinal findings are abnormal is dangerous, for it suggests that retinal damage precedes the elevated blood pressure rather than is caused by it. That the latter phenomenon is common obviously cannot be denied. Long-term follow-up on these young girls is essential to prove the point. Unfortunately, the decision as to the normality or abnormality of the optic fundus is all too frequently based on the level of arterial pressure. The significance of these retinal findings in these young girls is unknown. A study to ascertain whether a higher percentage of these girls will develop hypertensive vascular disease is now under way, as is a study to determine the frequency of these findings in the young healthy normotensive males and females of the Caucasian race. Is this another period of normotension in the life of the hypertensive patient that Perrera [5] refers to?

Hypertensive Vascular Disease Plus Superimposed Toxemia

There were 90 patients in this group and all had a history of hypertension antedating their pregnancy. Examination of the retinae revealed the chronic changes of hypertension (increased light stripe, tortuosity and arteriovenous nicking), and also showed the generalized retinal sheen characteristic of toxemia (to be discussed in detail elsewhere). Congestive heart failure was not seen.

When seen during the first trimester of pregnancy, these patients differed in no way from those who were hypertensive. The fundi showed hypertensive retinopathy with no retinal sheen; the arterial blood pressure was at the level of the nonpregnant state or lower, and signs or symptoms of toxemia were not present. Whereas signs of toxemia most frequently develop in the eighth or ninth month of pregnancy in the group with true toxemia, in this group signs of toxemia frequently developed in the fourth or fifth month of pregnancy.

A generalized retinal sheen, the first sign of superimposed toxemia, appeared in 33 patients in the middle of the fourth month, in 41 patients at five and one-half months, and in 26 patients at seven and one-half months. Elevation of arterial pressure (particularly the diastolic), edema and albuminuria appeared two to four weeks after the appearance of the retinal sheen, each sign increasing in severity in the subsequent month if not controlled by drug therapy. The level of arterial pressure at the height of the toxemic process was higher than in the hypertensive group and the group with true toxemia.

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A generalized retinal sheen, the first sign of superimposed toxemia, appeared in 33 patients in the middle of the fourth month, in 41 patients at five and one-half months, and in 26 patients at seven and one-half months. Elevation of arterial pressure (particularly the diastolic), edema and albuminuria appeared two to four weeks after the appearance of the retinal sheen, each sign increasing in severity in the subsequent month if not controlled by drug therapy. The level of arterial pressure at the height of the toxemic process was higher than in the hypertensive group and the group with true toxemia.

Three days after delivery the arterial pressure returned to the usual nonpregnant level in 61 patients, and remained essentially the same in 29 patients. At three weeks post partum there was little change in blood pressure but there was no edema, and the retinal sheen that had been present in all at the height of the toxemic process was absent in 49 patients.

At six weeks post partum the blood pressure had returned to the usual nonpregnant level in 21 patients, and the retinal sheen had disappeared in all patients, leaving pure hypertensive retinopathy. Edema was absent in all patients, and albuminuria was present in only the one patient who had consistently shown albuminuria prior to pregnancy. The arterial pressure in the remaining eight patients has remained significantly above the usual nonpregnant level for one year postpartum.

Comment

These are the sickest patients. The blood pressure is higher than in the pure toxemia group, and the superimposed toxemia is usually of the severe type. Our data also confirm that toxemia appears earlier in the true hypertensive patient.[6] The management of such patients presents a particularly difficult problem, since the life of the fetus is always in jeopardy at this midstage of pregnancy. Early recognition of the superimposed toxemia is therefore essential. Since the appearance of the generalized retinal sheen precedes the other, more obvious signs of toxemia (rising blood pressure and edema) by two to three weeks, its prompt recognition gives the physician an advantage in instituting therapy. Frequent ophthalmoscopic examinations in the hypertensive pregnant patient are therefore mandatory.

Postpartum Hypertension

This group can readily be divided into: (1) those who show a rise in arterial pressure in the first 24 hour postpartum period, and (2) those who show a rise in arterial pressure for the first time from three to six weeks post partum. *Twenty* patients were in the first group and *52* in the second. All had a completely normal pregnancy and an uncomplicated delivery, with no signs or symptoms of toxemia or hypertension, and history of previous toxemia or hypertension was denied by all. Ophthalmoscopic examination was normal in all.

In the *20* patients who developed a rise in arterial pressure in the immediate postpartum period, *16* had received oxytocin (Pitocin) after delivery. The blood pressure returned to normal in all patients before discharge (three or four days postpartum).

In the second group, besides a normal antepartum course and delivery, there was also a normal immediate postpartum course. The only abnormality in this group was an abnormal blood pressure reading (recorded at three consecutive office visits). By three months postpartum the arterial pressure had returned to normal in *40* patients, and at six months post-

partum the arterial pressure had returned to normal in 10. The average blood pressure in this group was 170/110 mm. Hg. By the end of a year not a single patient showed an elevated blood pressure reading.

Comment

Why does the arterial pressure become elevated in this period? In the immediate postpartum period, a hypertensive reaction to an oxytoxic agent may account for some elevated blood pressure readings. In this respect, oxytocin is less hypertensive than methyl ergonovine, in our experience. As mentioned above, the group of hypertensive patients who became normotensive during pregnancy accounts for a fair percentage of cases of "postpartum rises." (These cases are not included in this group, however, since their fundi show hypertensive changes.)

The use of oxytoxic agents in no way explains the elevation of pressure in the second group. Stout,[7] Meyer and Nadler[8] and Dieckmann[3] have reported this phenomenon. No explanation has been given. It is interesting that the arterial pressure in a chronic hypertensive patient is frequently the highest during this period. Whether this is related to a hormonal imbalance is not known.

Since in our experience the blood pressure returns to normal in most patients by six months, and in all by the end of a year, from a practical point of view treatment is not necessary. From a scientific standpoint, an evaluation of any drug given during this period is obviously worthless. Whether this is the beginning of hypertensive vascular disease in these patients can be answered only by long-term follow-up studies.

Pyelonephritis

Fifty-six patients fell into this group: 41 were ante partum and 15 post partum. The antepartum patients were all referred because of "toxemia" and the postpartum patients because of "albuminuria." Albuminuria was present in all cases. In 20 of the antepartum cases the arterial pressure was slightly elevated (average, 150/100 mm. Hg). Ankle and pretibial edema were present in 15 antepartum cases. Examination of the retinae was normal in every instance. None of the patients complained of fever, costovertebral angle or suprapubic pain, or burning or frequency of urination.

Microscopic urinalysis revealed clumps of white blood cells in all cases. Glitter cell stains were positive in *49* and urine culture revealed pathogens in *56*. Therapy with the appropriate antibiotics caused prompt clearing of the "toxemia" in the antepartum patients and disappearance of the albuminuria in the postpartum cases.

Comment

Even in the best obstetric clinics, microscopic urinalysis is not part of the routine procedure. Without a microscopic urinalysis, the finding of

albuminuria, edema and an elevated arterial pressure would most assuredly be diagnosed as toxemia.

The presence of albuminuria and the absence of a retinal sheen in a pregnant patient suggest pyelonephritis and necessitate a microscopic urinalysis. From an internist's standpoint, the significance of the early recognition and prompt therapy of pyelonephritis in the prevention of chronic disease and subsequent hypertension cannot be overemphasized. This is a treatable type of toxemia and a preventable type of hypertension. A more detailed analysis of our pyelonephritis cases will be presented elsewhere.[9]

Pure Toxemia

The diagnosis in 154 patients was true toxemia. This was characterized by a rise in diastolic blood pressure and/or edema, and/or albuminuria, and the sign par excellence, a generalized retinal sheen (a wet, glistening appearance of the entire fundus).

All of our patients were under 20 except one. Their ages ranged between 11 and 22, with an average of 16.5 years. No abnormalities were seen during the first five months of gestation. The arterial blood pressure remained normal, there was no abnormal weight gain, no edema and no albuminuria, and examination of the optic fundi showed them to be consistently normal. At some time between six and one-half and seven and one-half months, a generalized retinal sheen developed, though the blood pressure remained normal and no manifest signs of toxemia were present (no edema or albuminuria). At seven and one-half months the arterial pressure, particularly the diastolic pressure, increased (from 60 to 80 mm. Hg, or from 70 to 90 mm. Hg), edema and albuminuria made their appearance, and the retinal sheen became more prominent. At term, or before if induction of labor was deemed advisable, the full-blown picture of toxemia was present, with an elevated diastolic pressure, facial and peripheral edema, albuminuria and a prominent retinal sheen.

At three weeks post partum the arterial pressure was usually falling, edema had disappeared, albuminuria had disappeared in all but four patients, and the retinal sheen, though still present, was diminished. At six weeks post partum, *125* patients had no symptoms and showed no signs or residuals of toxemia. The blood pressure was normal, edema and albuminuria were absent, and the retinal sheen had disappeared. In *29* patients, however, though the blood pressure had returned to normal and the manifest signs of toxemia had disappeared, examination of the retinae revealed that the retinal sheen was now replaced by definite grade 1 or grade 2 retinopathy. Seventeen of these patients have now been followed for 30 months. The retinopathy has remained unchanged, although the blood pressure has continued to be normal.

Comment

Although the diagnostic and prognostic value of the ophthalmoscopic examination has been well established in hypertensive vascular disease, a confusing literature has arisen concerning the fundus findings in toxemia of pregnancy—confusing, as Gordon [10] says, because many authors have failed to differentiate those changes due to long-standing hypertension and those findings that occur purely by virtue of the existence of a toxic process in the course of pregnancy.

Writers around the turn of the century, such as Silex,[11] Miller [12] and Zangemeister,[13] when reporting on ophthalmoscopic changes in toxemias, referred to hemorrhages, exudates and papilledema, undoubtedly describing long-standing grade 3 and grade 4 hypertensive retinopathy, which had nothing to do with toxemia per se.

During the past few decades the much more frequently encountered retinal changes—classified as grade 1 or 2—have been recognized and reported. Haselhorst and Mylius,[14] Masters [15] and Hallum [16] all recognized that severe toxemia was frequently associated with spasm of the retinal arteries, whether transient or persistent, localized or diffuse.

Mussey and Mundell [17] and Wagener and Keith [18] documented the presence of arteriolar retinal spasm in toxemia, and stressed its importance, especially as being distinguished from true retinopathy. More recently, Hallum,[19] and particularly Landesman and his associates,[20] have emphasized the necessity for frequent retinal examination for the intelligent management of toxemia patients. Landesman has conclusively shown that the advancement of retinal arteriolar damage (meaning spasm) was directly correlated with the fetal death rate, and that the development of spasm or increase in its severity may frequently institute an indication to terminate the pregnancy for the welfare of both mother and baby.

In true toxemia the retinal vessels are entirely normal, except for segmental vasospasm. There is no increase in the arterial stripe, no tortuosity and no arteriovenous nicking. In a particularly fulminating toxemia—as in any acute hypertensive state—flame-shaped hemorrhages and cotton-wool exudates may occur. We have seen this phenomenon only twice. In both instances the retinopathy had entirely cleared three weeks postpartum. We are in firm agreement with Landesman,[20] Wagener,[18] Masters [15] and Hallum [16] that the appearance of exudates or hemorrhages is a grave sign and an indication for induction of labor or cesarean section.

Though the vessels are normal in toxemia, the entire retina has a wet, glistening appearance; it seems to be covered by a thin film of fluid. This film of fluid, though generalized, is seen best along the course of the blood vessels. The retinal sheen, because of its fluid nature, causes many reflections of light when the ophthalmoscope is focused on the fundus. The examiner therefore has difficulty in clearly outlining the retinal vessels; the

more pronounced the sheen, the more severe the toxemia, the greater the difficulty. The many reflections of lights on a wet street at night resemble this phenomenon. The shiny, wet sheen has the glistening appearance of the normal tympanic membrane.

The retinal sheen is not a specific finding for toxemia of pregnancy, for it is also seen in acute nephritis (which simulates toxemia more closely than any other condition) and the nephrotic phase of glomerulonephritis. It is not seen in congestive failure or the edematous state due to liver disease. The retinae of children and young adults frequently have a wet, shiny appearance, but this wetness is always limited to the temporal portion of the retina and seldom, if ever, crosses over to the nasal portion. If it does, it is seen only immediately adjacent to the disc. The appearance of the retinal sheen of toxemia differs in no way from the normal phenomenon, except in degree and extent. The normal wetness is localized, the abnormal, generalized.

The real importance of the retinal sheen is that it is not seen in hypertensive vascular disease and, in our experience, is usually present in true toxemia. Just as papilledema is the best sign of malignant hypertension, although not restricted to that disorder, so the retinal sheen is the best sign of toxemia of pregnancy. The significance of this phenomenon is not known, but it probably represents superficial retinal edema, a consequence of the generalized vasospasm characteristic of toxemia. As the toxemia increases in severity, the retinal sheen becomes more obvious, and as the toxemia subsides, the retinal sheen disappears. In this regard, we have seen disappearance of the sheen in a matter of hours following parenteral veratrum in hospitalized patients, and decrease or disappearance of sheen in a matter of days following diuretic and/or hypotensive therapy on an outpatient basis. Contrariwise, a completely asymptomatic and apparently healthy 18 year girl in her eighth postpartum month following full-blown eclampsia, who is currently being followed in our clinic, still demonstrates a definite retinal sheen. No explanation can be given. We feel that the index of severity of the toxemic state is best followed by frequent ophthalmoscopic examination. When the sheen is increasing, even though the arterial pressure is falling or peripheral edema decreasing, more definitive therapy is indicated. Similarly, if the sheen is regressing, despite a rising arterial pressure, temporizing measures are in order.

It will be noted that, in an attempt to examine patients before the onset of toxemia, young normal primigravid patients were referred to the clinic. Weekly examination of this group frequently disclosed the retinal sheen as the only abnormality, i.e., albuminuria, edema and hypertension were not present. The findings in these patients therefore afforded an opportunity to judge the accuracy of the retinal sheen in predicting toxemia. In only two of the 34 patients in whom a sheen was demonstrated did full-blown toxemia fail to develop. From the false-negative point of view, only three

patients in whom we would definitely have diagnosed toxemia failed to show a generalized retinal sheen. While not infallible, the retinal sheen seems to be a most useful adjunct in predicting and corroborating the diagnosis of toxemia.

Finally, it should be noted that in presenting our diagnostic criteria for true toxemia we used the phrase "a rise of diastolic blood pressure," rather than a specific level of diastolic pressure. Although the conventional 140/90 mm. Hg may well be the upper limit of normal for the group of women 25 to 35 years old, a diastolic pressure of 90 mm. Hg is certainly abnormal for the majority of women under 20 years of age. In our experience, the average diastolic blood pressure in the group under 20 is 60 to 70 mm. Hg at three to four months gestation, and the pressure remains at this level if the pregnancy remains uncomplicated. It is apparent, therefore, that a rise in diastolic pressure from 60 to 80 mm. Hg, or from 70 to 90 mm. Hg, is very significant in an individual patient—indeed, as significant as a rise in diastolic pressure from 80 to 100 to 110 mm. Hg. The cases of eclampsia reported as occurring with a normal blood pressure undoubtedly fall into this category.

Generalized Edema Without Disease

Thirty-eight patients fell into this group. Their ages ranged between 17 and 34. In each there was a history of intermittent edema of the dependent type, particularly in the midcycle and premenstrual period, involving the ankles, pretibial region, hands and face. During the first trimester of pregnancy the edema began to increase in severity and continued to do so until delivery. Unlike the nonpregnant state, however, eight to 12 hours of rest would not clear the edema entirely.

The edema was the only abnormality in these patients. The arterial pressure remained normal, albuminuria did not occur, and ophthalmoscopic examination was consistently normal. Following delivery the edema decreased in severity, so that by three weeks postpartum, 12 hours of recumbency would again entirely eliminate edema from the ankles and pretibial region.

Since serum sodium determinations and salt-loading studies were not done in these patients, only conjectural statements can be made concerning the etiology of this state. In all probability these patients are the pseudopreeclampsia patients described by Dieckmann.[3] The original cause of the edema is unknown. Its worsening during pregnancy may be explained in part by certain mechanical features, i.e., blockage of venous drainage from legs by the uterus, and increased blood volume in the legs. These factors fail, however, to explain the increased edema in the hands and face.

From a practical point of view the edema can be satisfactorily controlled by diet and intermittent diuretic therapy. Diamox has been particularly effective in this regard. The fact that hypertension and albuminuria have

not developed in these patients (even in the untreated ones) and the retinal sheen was consistently absent suggests (1) that this edematous state is not closely related to or the forerunner of toxemia, and (2) that the retinal sheen is a fairly specific sign for toxemia.

Unrelated Cardiac and Kidney Disease

Five patients were in this group. Three were diagnosed as rheumatic heart disease and two as chronic glomerulonephritis.

Two of the rheumatic heart disease patients had mitral stenosis and regurgitation; the other had aortic regurgitation and mitral regurgitation. All of these patients prior to pregnancy had been in mild congestive failure requiring digitalis. A 200 mg. sodium diet was the only additional therapy needed to control the congestive failure. No aggravation of symptoms or of the cardiac state was noted during pregnancy or delivery.

The two patients with chronic glomerulonephritis were known to have albuminuria, microscopic hematuria and granular casts prior to pregnancy. Both had histories of previous premature deliveries. The arterial pressure and albuminuria increased in both patients during the fourth month of gestation and, fortunately, both went into labor spontaneously in the same month.

Discussion

Although the findings of an elevated blood pressure and/or albuminuria and/or edema in a pregnant patient are consistent with the diagnosis of toxemia of pregnancy, they are by no means diagnostic of this condition. Besides toxemia, the diagnostic possibilities include hypertensive vascular disease, hypertensive vascular disease plus toxemia, pyelonephritis and glomerulonephritis. An ophthalmoscopic examination and complete urinalysis enable the physician to differentiate these disease states promptly. Table 3 shows that toxemia is present when the ophthalmoscopic examination reveals a retinal sheen and normal arteries, and urinalysis reveals only albuminuria. Hypertensive vascular disease exists when the retinal arteries show hypertensive changes, and no retinal sheen is present. When both hypertensive changes and a retinal sheen are seen on ophthalmoscopic examination, with or without albuminuria, toxemia is then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggests pyelonephritis; clumps of white cells and glitter cells document the diagnosis. Though a retinal sheen and albuminuria are seen in both toxemia and acute glomerulonephritis, microscopic hematuria (occasionally gross hematuria) is seen only in glomerulonephritis.

Differentiation of these disease states has more than academic interest. From the practical standpoint, it is reassuring for the physician to find hypertensive changes and fail to find a retinal sheen in a pregnant patient with an elevated blood pressure reading. This patient does not have

toxemia. She can be treated in the same fashion as though she were nonpregnant. On the other hand, the development of a retinal sheen in the same patient—or, for that matter, in any patient—necessitates prompt therapy. The importance of early recognition (particularly differentiation from toxemia) and prompt treatment of pyelonephritis cannot be overemphasized.

Only after the correct diagnosis has been made can one attempt to answer whether toxemia causes permanent vascular damage. The main reason for confusion, as Dieckmann [3] has said, has been a mistaken diagnosis during pregnancy—for example, a diagnosis of toxemia when hypertensive vascular disease was actually present. Experience in our clinic attests to this, for, although 95% of the patients referred to our clinic were originally diagnosed as toxemia, only *13%* of the patients had toxemia by our criteria.

TABLE 3

Differential Diagnosis of Toxemia

TOXEMIA ← ELEVATED B.P. / ALBUMINURIA / EDEMA

	OPHTHALMOSCOPIC EXAMINATION		URINALYSIS		
	Retinal sheen	Retinopathy	Alb.	W.B.C.	R.B.C.
PURE TOXEMIA	√	0	√	0	0
H.V.D.	0	√	±	0	0
H.V.D. + TOX.	√	√	√	0	0
PYELONEPHRITIS	0	0	√	√	0
GLOMERULO-NEPHRITIS	√	0	√	√	√

Unless an accurate diagnosis is made originally, follow-up studies are obviously worthless. Furthermore, it is incorrect, without serial studies, to attribute hypertension, retinal changes or renal impairment to a toxemic pregnancy that occurred five or more years previously.

How, then, can one attribute vascular damage to toxemia? The finding of definite retinopathy in 29 of our toxemia patients at six weeks postpartum whose retinae were entirely normal prior to the toxemic episode certainly suggests cause and effect. In these patients the following sequence was seen: (1) normal blood pressure with normal fundi and no manifest signs of toxemia at three months' gestation; (2) elevated blood pressure with a generalized retinal sheen, edema and albuminuria at the height of toxemia; and (3) normal blood pressure, definite retinopathy (grade 1 or grade 2 hypertensive changes) and no manifest signs of toxemia at six weeks postpartum. These patients now have vascular disease without hypertension

or any obvious renal impairment. The retinal changes seem to be permanent, since no regression has been noted in 11 patients followed for more than two and one-half years.

Why in *29* patients with true toxemia retinal changes developed and in *125* these changes did not develop is unknown. As Dieckmann [3] says, it is illogical to think that there are two types of preëclampsia—eclampsia, indistinguishable clinically, one causing vascular damage, the other not. Severity of toxemia does not seem to be the deciding factor in determining whether vascular damage is to follow, for, if this were so, a much higher incidence of vascular damage would be seen after eclampsia. Page and Cox,[21] Dieckmann [3] and Chesley [22] have found that toxemias without convulsions are associated with a higher incidence of permanent vascular renal damage than actual eclampsia. Retinal examination in 19 of our 23 patients with eclampsia was normal at six weeks postpartum.

Experience in our clinic coincides with that of Gibberd,[23] Peckham,[24] Chesley [22] and others,[3] who maintain that the longer the duration of the first toxemia, the greater the incidence of vascular damage. The average duration of the toxemic process (uncontrolled by therapy) in the group that ultimately showed retinal changes was 6.1 weeks; the average duration of toxemia in the other group was 2.5 weeks. Undoubtedly the reason that so many patients who have eclampsia escape vascular damage is that they are treated promptly and intensively.

From the long-range standpoint, it would seem that it is better to have "a lot of toxemia for a short time than a little toxemia for a long time." It would also seem that, once the stage of viability of the fetus has been reached, there is no advantage in allowing a toxemic pregnancy to continue beyond two weeks if uncontrolled by therapy. Since a patient with mild toxemia is not clinically sick and presents no immediate problem, the seriousness of the disease is not realized. A conservative course is frequently decided upon in the hope that the fetus will grow in size, or at least mature. In our experience, once toxemia is present, the fetus does not grow in size, and each week the toxemic state is allowed to continue (even if manifested by only retinal sheen and 1 plus albuminuria), the incidence of vascular damage to the mother is increased.

Though the theory is certainly unproved, it is attractive to hypothesize that the generalized vasoconstriction characteristic of toxemia, and most readily determined by the funduscopic examination, if allowed to continue beyond a critical period (more than one month), causes definite vascular damage. At first, the only residual evidence of the vasoconstriction may be retinopathy; the arterial pressure may be normal. It is at this stage that these patients are seen from the sixth week to two years postpartum.

Summary

Serial studies on 1,081 "toxemia-suspect" patients have revealed that hypertensive vascular disease and pyelonephritis frequently masquerade as

toxemia of pregnancy. The triad (or any part) of an elevated blood pressure, edema and albuminuria has been seen in each of these diseases. Experience has suggested that ophthalmoscopic examination and a complete urinalysis permit prompt differentiation of these diseases.

Toxemia is said to exist when the ophthalmoscopic examination reveals a retinal sheen and normal arteries, and urinalysis reveals only albuminuria. Hypertensive vascular disease exists when the retinal arteries show hypertensive changes and no retinal sheen is present. When both hypertensive changes and a retinal sheen are seen on ophthalmoscopic examination, with or without albuminuria, toxemia is then superimposed on hypertensive vascular disease. The finding of normal fundi and albuminuria suggests pyelonephritis; clumps of white cells and glitter cells document the diagnosis. Though a retinal sheen and albuminuria are seen in both toxemia and acute glomerulonephritis, microscopic hematuria (occasionally gross hematuria) is seen more commonly in glomerulonephritis.

Though 95% of the patients referred to the clinic were originally diagnosed as toxemia, only 13% had toxemia by our criteria. Our diagnoses included hypertensive vascular disease (666), hypertensive vascular disease plus superimposed toxemia (90), postpartum hypertension (72), pure toxemia (154), pyelonephritis (56), edema without disease (38), and unrelated cardiac or renal disease (five).

The ability to differentiate these disease states provided the opportunity to study whether toxemia caused vascular damage. One hundred twenty-five of the pure toxemia group six weeks postpartum revealed no abnormality. In 29 patients, however, despite return of the blood pressure to normal and disappearance of edema and albuminuria, examination of the retina revealed definite retinopathy. These retinal changes are attributed to the duration of the toxemia rather than to its severity.

SUMMARIO IN INTERLINGUA

Un experientia trienne con 1081 patientes suspecte de toxemia ha revelate que le constatationes de elevate pressiones sanguinee e/o albuminuria e/o edema in un patiente pregnante, ben que illos es compatibile con le diagnose de toxemia de pregnantia, non es del toto diagnostic pro iste condition. A parte toxemia, le possibilitates diagnostic include morbo vascular hypertensive, morbo vascular hypertensive plus toxemia, pyelonephritis, e glomerulonephritis. Le examine ophthalmoscopic e un complete urinalyse permitte al medico le prompte differentiation de iste statos morbide. Toxemia es presente quando le examine ophthalmoscopic revela un lustro retinal e arterias normal durante que le urinalyse revela solmente albuminuria. Morbo vascular hypertensive es presente quando le arterias retinal monstra alterationes hypertensive in le absentia de lustro retinal. Quando tanto alterationes hypertensive como etiam lustro retinal es observate sub le examine opthalmoscopic, sin reguardo al presentia o absentia de albuminuria, toxemia es superimponite a morbo vascular hypertensive. Le constatation de fundos normal e de albuminuria es indicative de pyelonephritis; cumulos de cellulas blanc servi a corroborar le diagnose. Ben que lustro retinal e albuminuria se trova in toxemia e etiam in glomerulonephritis, hematuria microscopic (a vices mesmo hematuria grossier) es presente solmente in glomerulonephritis.

Ben que 95 pro cento del patientes referite a nostre clinica habeva originalmente recipite diagnoses de toxemia, solmente 13 pro cento habeva toxemia secundo nostre criterios. Nostre diagnoses includeva morbo vascular hypertensive (666 casos), morbo vascular hypertensive plus superimposition de toxemia (90 casos), hypertension post parto (72 pasos), pur toxemia (154 casos), pyelonephritis (56 casos), edema sin morbo (38 casos), e non-affin morbos cardiac o renal (5 casos).

Nostre capacitate a differentiar inter iste formas de morbo rendeva possibile studiar si toxemia causa lesiones vascular. In 125 casos de pur toxemia nulle anormalitate esseva constatate sex septimanas post parto. In 29 patientes, ben que le pression sanguinee habeva retornate a nivellos normal e ben que edema e albuminuria habeva disparite, le examine del retina revelava un definite retinopathia. Iste alterationes retinal es attribuite per nos al duration del toxemia plus tosto que a su severitate.

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CASE REPORTS

HYPONATREMIA IN PRIMARY MYXEDEMA *

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In former years it was believed that the varieties of myxedema could be clinically recognized. This was later found not to be so, and the difficulties involved were better realized. The case being reported presents two unusual problems: first, the problem of the differential diagnosis between primary myxedema and that of myxedema secondary to pituitary dysfunction; second, the severe electrolyte disturbance existent in this patient.

Case Report

A 66 year old female was admitted to Mount Zion Hospital on January 11, 1953. Her present illness had probably begun 10 years prior to this admission and three years prior to her San Francisco City and County Hospital admission in 1946, when she had stated that she had noticed puffiness of her eyes and progressive loss of scalp hair in 1943, coincident with her menopause. She had had a low voice all her life but, aside from complaints of weakness, hair loss and periorbital edema, her history then was noncontributory. Laboratory examination at that time revealed a serum cholesterol of 680 mg. per 100 ml. and a basal metabolic rate of minus 28%. The patient was treated with 0.25 grain of thyroid extract daily, and this dosage was increased to 1 grain daily at the time of discharge. On this regimen she lost 20 pounds and her cholesterol was reduced to a normal value. After discharge she soon stopped taking thyroid medication and had not taken the medication during the interim between discharge from San Francisco City and County Hospital and admission to Mount Zion Hospital.

The patient was too lethargic to give a valid history, nor could her family assist in this regard. It was ascertained from her that she had never been able to become pregnant. Family history seemed to be noncontributory.

Physical examination revealed an elderly, obese female (171 pounds), oriented but sluggish in movement and speech. Her voice was low and her pronunciation thick. The scalp hair was thin, and was absent in the frontal region of the head (figure 1). Axillary, pubic, eyebrow and eyelash hair were absent. There was generalized soft but nonpitting edema, the periorbital areas being particularly involved. Malar flush was present. Other pertinent findings were as follows: The gums were hypertrophic and bled easily. There was minimal enlargement of the tongue. There were subcrepitant basilar râles at both lung bases posteriorly. The heart was enlarged to percussion 1 cm. outside the midclavicular line; the second apical sound was louder than the first, and the second sound was louder over the aortic area than the pulmonic; no shocks, thrills or murmurs were noted, and the heart rate was 50 and regular; blood pressure, 160/120 mm. of Hg. The abdomen

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was obese and no organs were palpated. There was a sluggish response of deep tendon reflexes.

Laboratory work on admission was as follows: hemoglobin, 10 gm. per 100 ml.; erythrocytes, 3,680,000; leukocytes, 7,500, with a normal differential count. Urinalysis: 4 plus albumin, which albuminuria persisted to a lesser degree throughout her course; a urine specific gravity was 1.020 on 1/22/53 when the albuminuria was 2 plus. Other laboratory work pertinent to endocrine and renal function was as follows: serum cholesterol, 483 mg. per 100 ml.; bilirubin, 1.00 mg. per 100 ml. (0.15/0.85); icterus index, 6; total serum proteins, 6.1 gm. per 100 ml. (3.4/2.7); basal metabolic rate, minus 30%; protein-bound iodine, 2.0; I^{131} uptake, 7% both before and after three day stimulation with 20 USP units daily of thyrotropic hormone; follicle-stimulating hormone, negative at 5 and 50 units; phenolsulfonphthalein, 72%

FIG. 1.

excretion in two hours; creatinine clearance, 43.7 c.c. blood cleared/min.; blood nonprotein nitrogen, 14 and 18 mg. per 100 ml.; blood urea nitrogen, 7.5 mg. per 100 ml. Other laboratory data are listed in table 1. Striking hyponatremia and hypochloremia are evident.

Course: There was little change in physical status until January 20, at which time she was observed to be less responsive than previously. Her appetite, which had been good, became poor at this time. She was treated supportively and an attempt was made to balance her severely abnormal serum electrolytes using isotonic saline solution. On January 22 she was given one dose of 1/10 grain of USP thyroid. On the following day she was given one dose of 0.25 grain of thyroid. The patient's condition continued to deteriorate and she died two days after thyroid therapy was started. (ACTH had been administered as follows: 25 units intravenously over a four hour period on January 17 and January 19, and 2 c.c. (160 u)

of Wilson gel intramuscularly on January 21. The ACTH was administered as a diagnostic measure.)

Autopsy Findings: * The body was that of a white adult female weighing approximately 180 pounds and measuring five feet six inches in length. The hair of the head was dark gray and extremely sparse, being reduced in general to an average of 10 hairs per square centimeter of scalp. The eyebrows and axillary and pubic hair were absent. There was a generalized edema throughout the body, with the face, lips and eyelids particularly edematous. There was a well developed arcus senilis bilaterally. There was an atrophy of the soft tissue of the gums. The tongue was slightly enlarged and the lips were extremely thickened. The extremities showed the same type of nonpitting edema that was present throughout the body. The nails were coarse. Ecchymoses were present on the anterior aspect of the lower extremities.

The important gross findings other than those apparent were: All the retroperitoneal tissues were extremely edematous, containing colorless gelatinous fluid. There was a reduced volume of muscle tissue; this tissue was soft, had a salmon

TABLE 1

Date Jan.	Serum; mEq./L.				Urine						
	Na	Cl	CO_2	K	Volume c.c./ 24 hr.	Na mEq./ L.	Cl (as NaCl) mEq./L.	Nitrogen gm. per 24 hrs.	17 K.S. mg. per 24 hrs.	Creatinine mg. per 24 hrs.	Comp. F mg. per 24 hrs.
13					1,075					800	
15	110	71.4									
16	110	70.6	22.7	3.5	1,100				9.6		
17			18.7		562		17.2	3.6	2.7*	535*	6.1*
18						8.8			14.1		
19	105	62.6		4.0							
20					470	2.8	12.9	3.3			
21					510	1.6			6.7		
22					375				4.2*†	348*†	24.4*†
23					375	1.8	6.9	3.1	9.2		

* Performed at University of California Metabolic Unit, courtesy of P. H. Forsham, M.D.
† After ACTH—25 mg. I.V. 8 hr.

color and was edematous. Each hemithorax contained 350 c.c. of clear yellow fluid; the pericardial sac contained 150 c.c. of dark yellow fluid; the abdominal cavity contained approximately 5 L. of clear yellow fluid. The heart weighed 520 gm., and a 2 cm. soft, depressed area was noted on the anterior surface of the left ventricle. X-rays of the injected heart failed to show occlusion of the lumen in any of the coronary vessels, although occasional areas of moderate stenosis were present. There were widespread atheromata present throughout the aorta. The intestinal tract was normal. The kidneys and ovaries appeared normal. The brain showed some cortical atrophy and marked basilar vessel arteriosclerosis. The pituitary, adrenal and parathyroid glands were entirely normal. The thyroid gland weighed only 20 gm. and was composed of firm, fibrous white tissue, with nothing remaining which resembled normal thyroid parenchyma.

The pertinent microscopic findings were:

Thyroid (figures 2, 3): The gland was replaced by a moderately dense fibrous tissue; there were widely dispersed minute clusters of tiny follicles, some of which

* Performed by Dr. Milton J. Pearl and Dr. Gerson R. Biskind.

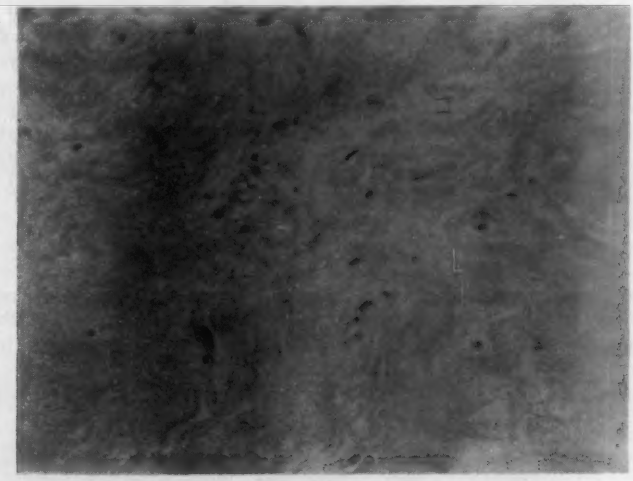

FIG. 2. Thyroid gland × 100. The usual follicles have been replaced by moderately dense fibrous tissue that is relatively acellular. A few small blood vessels can be found. The greater portion of the gland is represented by this type of tissue.

were surrounded by a few lymphocytes. The follicles were lined by a small cuboidal epithelial cell. There may or may not have been colloid in them. The fibrous tissue showed slight interstitial edema. All the small arterioles had greatly thickened walls.

Pituitary (figure 4): The anterior lobe was within normal limits as to size and cellular type. The eosinophilic cells were particularly prominent. The chromophobe

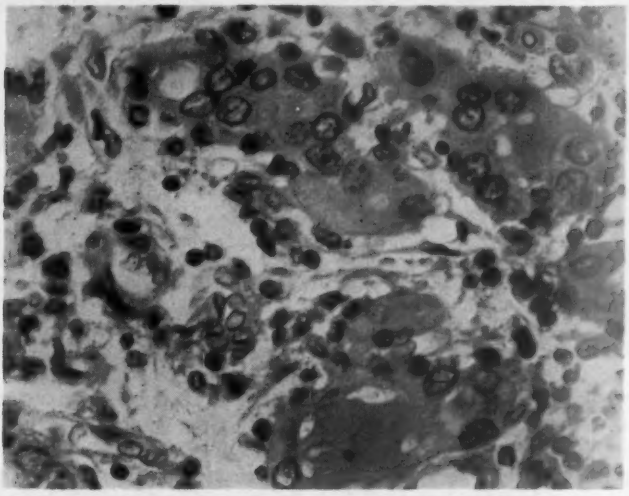

FIG. 3. Thyroid gland × 350. Remnants of shrunken follicles are seen. The colloid appears coagulated. A few lymphocytes are present. These follicles are characteristic of the very few that could be found in the entire gland.

cells appeared normal. The basophilic cells were not readily encountered. There was no evidence of degenerative scarring or other significant alteration. The posterior lobe was normal, and there were a few minute cysts indicating the intermediate lobe.

Adrenals: The adrenals had a thick, prominent cortex. There was slight interstitial edema. Most of the cortical cells had a deeply stained eosinophilic cytoplasm; relatively few had a vacuolated cytoplasm. In some regions the medulla was fairly prominent and contained a scattering of lymphocytes around the blood vessels. There were several isolated nodules of cortical tissue on the capsule.

Ovaries, Breast: There was atrophy of the ovaries and breast.

Kidney: The kidney showed arteriosclerotic focal scarring.

Hypothalamus: Multiple sections revealed no abnormality.

Heart: The heart showed focal old fibrous replacement of the myocardium; in other regions there was a questionable slight increase in the separation of the fibers, possibly due to fluid.

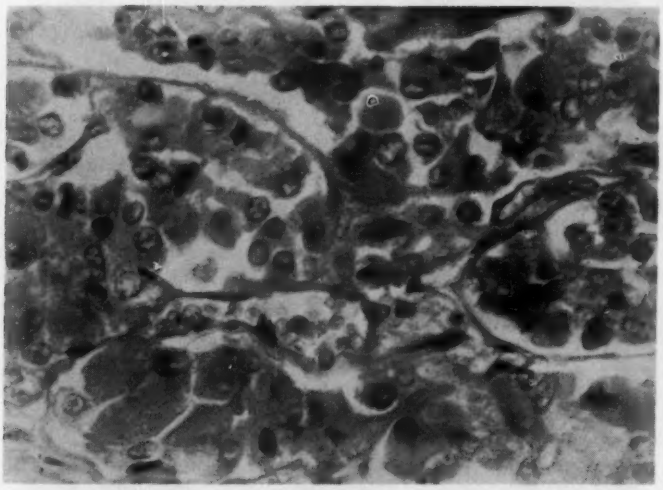

FIG. 4. Pituitary gland. The cellular elements of the anterior pituitary show distinctly outlined chromophils and chromophobes. Most of the large cells have a deeply stained eosinophilic cytoplasm (× 350).

Skeletal Muscle: The muscle fibrils showed a distinct separation that was probably the result of an increase in interstitial fluid. The individual fibers retained distinct intracellular staining characteristics.

DISCUSSION

Differential Diagnosis: Textbook discussions of myxedema formerly contained statements about the ease of differentiating the clinical aspects of primary myxedema from those of secondary myxedema. It was gradually realized that pituitary disease might, as its only secondary manifestation, result in the clinical picture of myxedema and that clinical differentiation from primary athyreosis might be impossible.[1] However, while it is agreed that clinical differentiation

cannot be made, many authors feel that laboratory studies can determine which of the two conditions prevails by revealing the functional status of other endocrine organs. In this case at least, final differentiation was made only at the autopsy table, although numerous laboratory studies were done. Many examples of the difficulty of laboratory differentiation are now in the literature. Tucker et al.[2] reported three cases of pituitary myxedema, in none of which was significant electrolyte disturbance noted. These authors considered the loss of genital function to be the outstanding feature distinguishing the three cases from primary myxedema. Despopoulos and Perloff,[3] studying 12 cases of primary myxedema, did gonadotropins in seven. The gonadotropins were increased in three cases, decreased in one and normal in three. Adrenal function as measured by 17-ketosteroids done in 11 cases was decreased in all cases. Serum sodium was determined in 11 cases, the lowest determination being 133 mEq./L. Statland and Lerman [4] reported a series of myxedema cases and emphasized in their discussion the difficulty of clearcut etiologic distinction; they pointed out that other endocrine functions (e.g., adrenocortical) might be depressed as a result of a primary myxedematous involvement of endocrine organs, and reported one of the cases with low serum sodium (126 mEq./L.) and chlorides in which a positive Cutler-Powers-Wilder test was obtained. Clinical and laboratory data in this case suggested depression of adrenal secretion of androgenic hormone, corticosteroids and electrolyte hormone. Means, Hertz and Lerman [5] also reported a series of cases of myxedema illustrating the difficulty, even with laboratory aids, of establishing the correct etiology of the myxedema (primary or secondary). The case being discussed further shows the inability of the laboratory to provide the diagnosis. Low serum sodium, low 17-ketosteroid excretion and absent urinary gonadotropins all suggest pituitary disease and secondary myxedema. Failure of thyroid stimulating hormone (TSH) to increase I^{131} uptake suggests primary myxedema.

Serum Electrolytes

The severe derangement of serum electrolytes in this case is probably the result of several factors. The possible mechanisms of such electrolyte alteration (hyponatremia and hypochloremia) may be considered under the following headings:

1. Salt loss in stool.
2. Salt loss in urine.
3. Water retention.
4. Shifts or compartmental redistribution of electrolytes and water.

Listed below are several diseases and physiologic alterations which might result in hyponatremia and hypochloremia. Some of these conditions (e.g., Addison's disease), when they exist, are proved causes of electrolyte disturbances.[6] Others are theoretic mechanisms which have been suggested by various authors. Thus resin therapy, diarrhea (e.g., pellagra [19]), inadequate intake (virtual loss) could result in salt loss in stool. Salt losing nephritis,[13–15] mercurial diuretics, Addison's disease, cerebral salt wasters,[17] pulmonary tuberculosis,[10] gout,[7] gastric carcinoma [11] and pneumonia [8, 9] could result in salt loss in urine, the latter six conditions possibly via indirect renal effect.[16] Increased

antidiuretic hormone (ADH) secretion,[20] inability to lose water through the skin, and heart failure (hypotonic retention [12]) could result in water retention. Finally, traumatic shock,[23-26] edema formation,[21] decreased base binding by serum proteins in cachexia [29] and reduction in cellular osmolarity [21] could result in compartmental redistribution of electrolytes and water. Most of the diseases and alterations listed above were not factors in producing the electrolyte disturbance in the reported case. Only those conditions which might have influenced the electrolyte pattern in this case will be discussed.

None of the diseases or alterations which might have caused salt loss in the stool was present. However, this patient may have had a meager salt intake for some time prior to admission.

In considering the second mechanism (salt loss in urine), it should be stated at the outset that there is no proof at all that this patient ever had a salt-losing condition. Urinary electrolytes were extremely low whenever measured (table 1). This might in part be due to the ACTH she received, but more likely it represents an agonal effect. There was, however, no clinical or laboratory indication of a salt-losing disease.

The third mechanism (water retention) comprises possible alterations which cannot be proved or disproved in this case. An increased secretion of antidiuretic hormone [20] might have been a continuous influence or primarily an intermittent one, responding to changes of plasma volume,[21] tonicity or oncotic pressure [22] of body fluids, body temperature, etc. In addition to the possibility of ADH over-secretion, the possibility of relative ADH excess exists in this case The generally impaired metabolism of the patient might have interfered with the elimination by liver and kidneys of a quantitatively normal amount of ADH. Whether the patient was able to lose water through the skin was not determined. Impaired renal function in myxedema was noted by Corcoran and Page,[18] who found alterations as follows: (a) decrease in renal blood flow, (b) decrease in glomerular filtration rate (GFR), (c) decrease in tubular secretory capacity, all of which disturbances returned towards normal after thyroid treatment. No electrolyte disturbances were noted in their cases. The low daily urinary output in this case (M.T.) was most likely due to impaired renal function, as just described.

The fourth mechanism involves compartmental redistribution of electrolytes and water. There is evidence to suggest that in both acute and chronic disease, local redistribution of electrolytes may occur; thus sodium may shift from the extracellular to the intracellular phase, and large increments of body electrolytes can be so "stored." When this factor is combined with the aforementioned theoretic dilution effect, marked hypo-osmolarity of the extracellular fluid might be the result. Also in this regard, Darrow [27] notes the occurrence of shifts of intracellular sodium to replace deficits of skeletal and cardiac muscle potassium. Tissue analyses were not made in this case.

The remaining theoretic reason for lowered extracellular osmolarity is a reduction in cellular osmolarity [21] secondary to metabolic aberration following upon myxedema and resulting in a shift of water out of the cells and a consequent dilution hyponatremia and hypochloremia. The decrease of cellular osmolarity is presumed to be a gradual process, which allows for a change in the "set of the center" [28] consequent to adaptation by the osmoreceptors.

Summary and Conclusions

1. An autopsied case of primary myxedema has been described.

2. The difficulties of differentiating this condition from pituitary myxedema, even with the aid of various laboratory determinations, are again illustrated.

3. Extremely low serum electrolytes were present in this patient. The mechanism for this is not known. It is felt that the abnormalities here were due to a combination of several factors, the most likely of which is a combination of compartmental redistribution of serum electrolytes and a water retention dilution of these electrolytes. A chronic dietary salt deficit probably accentuated the electrolyte derangement.

4. The most important fact derived in retrospect from a study of this case was that the clinical appearance of this patient was misleading upon admission. Initially she did not appear to be in any danger of decompensation, and was adjudged to be adjusted to her marked extracellular hypo-osmolarity. Then, suddenly her condition deteriorated possibly secondary to water intoxication. It would therefore seem preferable to treat such a patient as if she had pituitary myxedema, waiting to pursue definitive diagnosis until electrolyte balance is restored.

Acknowledgments

The author is greatly indebted to Gerson R. Biskind, M.D., Pathologist-in-Chief, Mount Zion Hospital, for his kindness in providing the entire autopsy interpretation and for photographing the microscopic sections.

Summario in Interlingua

Un femina de 66 annos esseva admittite al hospital con myxedema avantiate. Le historia del patiente pareva indicar que le condition habeva existite depost circa 10 annos. Un breve remission clinic habeva essite producite per medio de extractos thyroide, sed le patiente habeva tosto discontinuate iste medication e habeva habite nulle therapia durante septe annos ante su hospitalisation. Le examine physic al tempore del admission revelava le signos classic de myxedema. Le constatationes laboratorial includeva como punctos de interesse special: hyponatremia e hypochloremia, augmento de cholesterol seral, basse metabolismo basal e basse nivello de iodo ligate a proteina, basse acception de iodo radio-active sin melioration per hormon thyroido-stimulante, e un essayo negative pro hormon folliculo-stimulante.

Le stato physic del patiente non cambiava durante plus que un septimana. Postea illo se deteriorava subitemente, e le patiente moriva duo dies post le initiation de medication thyroide. Le examine post morte monstrava que le glandula thyroide esseva integremente reimplaciate per dense histos fibrose. Le glandula pituitari esseva completemente normal.

Le presente caso illustra de novo le difficultate del differentiation de myxedema primari ab myxedema secundari, mesmo per medio de extense tests laboratorial. Le caso es etiam notabile a causa del sever disturbation electrolytic que representa, secundo le informationes del autor, un situation unic in casos de myxedema primari. Le disordine electrolytic esseva probabilemente debite in parte a un effecto de dilution seral.

Le deterioration rapide del patiente post que su curso habeva essite relativemente stabile indica le situation precari de tal casos e sublinea le urgentia de prompte therapia pro myxedema pituitari.

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PROLONGED DIARRHEA WITH NEAR-FATAL HEMORRHAGE DUE TO HYPOPROTHROMBINEMIA *

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This report is concerned with a severe hemorrhagic disease which followed prolonged diarrhea. The patient presented as a medical emergency which was promptly relieved by appropriate therapy. Subsequent investigation established the diagnosis of sprue which had caused severe hypoprothrombinemia.

Several clinical features of this case deserve emphasis. The hypoprothrombinemia was so extreme as to endanger the patient's life. Further, the immediate medical problem was not characteristic of sprue, but was due to a rare complication of the abnormal physiology of this disease. The infrequency of severe purpura associated with diarrhea probably accounted for the delay in diagnosis. The importance of recognizing this problem, and of instituting suitable therapy, is well illustrated in the following case study.

Case Report

A 53 year old white housewife was admitted to the Albany Hospital July 7, 1952. The patient had noticed numerous small purpuric areas over the arms and legs for four days. This purpura had increased rapidly, and practically covered her body at the time of admission. She also complained of tarry stools the day of entry. For four years the patient had had diarrhea varying from three to 10 loose stools daily. Stools were nonbloody and foul-smelling but not greasy. She had lost about 20 pounds in four years. Several weeks before her hospital admission she had been seen by a gastroenterologist and a diagnosis of "irritable colon" had been proposed. At that time a few small purpuric areas were noted. She had been studied radiographically and all the studies were described as normal. Treatment with antispasmodics and low residue diet was unsuccessful. The remainder of the history was noncontributory. She gave no previous symptoms of a hemorrhagic disease, and she had not been out of the United States for many years.

Examination revealed a critically ill patient. Blood pressure was 90/60 mm. of Hg; pulse rate, 90; weight, 86 pounds. Temperature was 100.4° F. The skin over the trunk and arms was covered with confluent ecchymotic areas. The normal skin of the legs was almost completely replaced by diffuse, extensive subcutaneous hemorrhages (figure 1). Fundi were normal. There was no adenopathy. Thyroid was slightly enlarged. Heart and lungs were unremarkable. There was no enlargement

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of the liver or spleen. Rectal examination showed a grossly tarry stool, strongly positive for blood with benzidine dihydrochloride.

On admission, hemoglobin was 8 gm.; red blood cell count, 2,440,000 per cubic millimeter. The patient was seen in consultation the following day, at which time she was gravely ill. The count had dropped to a hemoglobin of 4.75 gm. per 100 ml.; red blood cell count, 1,650,000 per cubic millimeter, with a normal white cell count and differential. An immediate hemorrhagic disease study was ordered. Prothrombin time (one stage) was over four minutes and no clot was formed after 24 hours. A prothrombin time, using prothrombin free fresh plasma as a diluent, gave results similar to the one stage, undiluted prothrombin test. Bleeding time, platelet count and a test for circulating anticoagulants were all normal. Coagulation time (Lee-White) was markedly prolonged and failed to show any clotting after 24 hours of observation. A presumptive diagnosis was made of hypoprothrombinemia secondary

FIG. 1. Appearance of patient's skin showing extensive purpura.

to either prolonged diarrhea and impaired vitamin K absorption, or liver disease. As soon as the laboratory results were available, 75 mg. of vitamin K were given intramuscularly and 1,000 c.c. of banked blood were transfused. The following day the patient appeared markedly improved; prothrombin and clotting times were normal.

Additional laboratory studies showed FBS, 140 mg.%; nonprotein nitrogen, 36 mg.%. Total bilirubin was 0.4 mg.%. Bone marrow revealed marked erythrocytic hyperplasia, normoblastic in type. Further prothrombin times were all normal. Urinalysis was negative. Total proteins were 4.7 gm.%; globulin, 1.9 gm.%; calcium, 4.0 mEq.; phosphorus, 1.2 mEq. Cephalin flocculation was 3 plus. Blood culture and stool for ova and parasites were negative. Total cholesterol was 135 mg.%; esters, 70.5%. Oral glucose tolerance test (100 gm. of glucose) showed fasting specimen 92 mg.%, a peak of 158 mg.% one hour after the glucose, and 125 mg.% two hours after ingestion. Bromsulphalein, 5 mg./kg. dose, showed 2.5%

retention in 45 minutes. A gastrointestinal series was reported as negative, as was the small bowel and motility study. The pancreatic region showed no calcification. Two basal metabolism tests, on July 22 and July 24, were plus 40% and plus 45%. Protein-bound iodine was reported as 4.2 gamma %; unbound fraction, 2.1 gamma %. Amylase was 91 units/100 ml. Gastric analysis following histamine showed low values for free HCl and total acidity.

The patient was maintained on 5 mg. of vitamin K intramuscularly daily until July 25; vitamin C and ferrous sulfate were given orally. The purpura gradually cleared and the patient improved. Prothrombin times remained normal. On July 25 she was seen in consultation by an endocrinologist, who felt that there was no evidence for hyperthyroidism and that the clinical picture was best explained by pancreatic insufficiency. Duodenal intubation was performed by Dr. Paul Patterson, who reported that the secretions were similar to those found in sprue. The patient was discharged July 30, 1952. She was then followed with periodic office visits. She received no vitamin K until September 24, when the prothrombin time was 23 seconds. Hykinone orally, 10 mg. daily, was given until October 8, when the prothrombin time was 21 seconds. The patient was then placed on 10 mg. of Hykinone intramuscularly weekly. Prothrombin time on November 12 was 15 seconds. Hykinone was then administered every two weeks in a dosage of 10 mg. intramuscularly. The patient was given folic acid, 60 mg. daily by mouth for several weeks, and then 15 mg. orally per day. Parenteral B complex, dilute hydrochloric acid, Banthine and pancreatin were also tried in conjunction with a high protein, low fat diet. The diarrhea persisted and there was no consistent weight gain. She complained of persistent right leg pain and was rehospitalized in January, 1953. Prothrombin time and complete blood counts were normal. Neurologic consultation suggested previous purpura in the spinothalamic tract or brain as an explanation for the intractable leg symptoms. A paravertebral block was unsuccessful in relieving the symptoms.

On March 3, 1953, the patient was admitted to the Massachusetts Memorial Hospital under the care of Dr. Franz J. Ingelfinger. Various studies were performed which confirmed the diagnosis of nontropical sprue. The stool was light, greasy and foul, and contained 4 plus sudanophilic droplets after heating with acetic acid. Stool weights on admission were 200 gm. in 24 hours, which after therapy dropped to 70 gm. Two fasting blood sugars were 58 and 68 mg.% (normal). Two hours after 50 gm. of glucose by mouth the level was 72 mg.% (low). Serum carotene level on admission was 4.7 gamma % (extremely low). Vitamin A absorption studies showed very low results. The patient was placed on a Haas diet, eliminating all polysaccharides, as well as oral B complex and Synkayvite, 5 mg. daily; on March 31 blood carotene level was 20 gamma %. Pancreatic studies after intravenous secretin were borderline normal. Small bowel x-ray studies were reported as showing a sprue pattern. The patient's diarrhea subsided and she felt much improved on the therapeutic régime described. Sympathectomy was performed by Dr. Smithwick for the leg pain. She was discharged from the hospital on April 1 with a diagnosis of nontropical sprue. On April 10 the patient had a few loose stools and it was decided to try cortisone. She was given 150 mg. daily for one week and then 100 mg. daily. This was gradually reduced so that on June 16, 1953, when she was seen last, she was taking 25 mg. daily. Stools were normal (one daily), and the patient felt very well. Weight was 101 pounds, a 15-pound increase. Prothrombin time was 15½ seconds. The plan was to continue with the oral, water soluble-K and B vitamins, as well as 25 mg. of Cortisone daily in conjunction with the strict diet. The patient's hematologic values, prothrombin time and clinical status were to be followed periodically.

Comment

The clinical picture described, consisting of prolonged diarrhea and weight loss with the associated vitamin K deficiency, is very characteristic of sprue. The laboratory studies, including vitamin A absorption tests, serum carotene levels, stool examinations for fat, oral glucose tolerance test and small bowel x-ray studies, were all consistent with this diagnosis. This case represents sprue of the "nontropical" type, but it is generally agreed that classic sprue, idiopathic steatorrhea (nontropical sprue) and celiac disease are variants with similar abnormal physiology.[1, 2, 14]

The unusual clinical feature of this case was the massive bleeding which was exsanguinating the patient. This presented the emergency problem of therapy in a patient with unexplained purpura, the only clinical clue being a prolonged diarrhea. Laboratory studies revealed the clotting defect to be a marked deficiency in prothrombin (prothrombin time over 4 minutes, with failure to clot overnight). Normal platelets, elevation of the prothrombin time using prothrombin free plasma as a diluent, the absence of circulating anticoagulants, and the response to vitamin K therapy identified the hemorrhagic defect as a hypoprothrombinemia and excluded other clotting disorders. Therapy consisting of blood transfusions and vitamin K parenterally quickly reverted the clotting time and prothrombin times to normal.

Hypoprothrombinemia in association with sprue has been previously described, but the occurrence of frank hemorrhage and extensive purpura is most unusual. Ingelfinger [3] described two cases with purpura in nontropical sprue, one case having epistaxis and hematuria as well, with a prothrombin time under 1%. Kark et al.[4] reported one case with hematuria, purpura and melena, with a prothrombin time of 110 seconds and a clotting time of 20 minutes. Collins' [5] case report is interesting in that a patient with prolonged diarrhea developed hematuria and hemoptysis after being given sulfa orally. The prothrombin time was 41 seconds and returned to normal after vitamin K and whole blood were administered. It was suggested that in this situation the sulfa had interfered with vitamin K production in the bowel and contributed to the absorptive defect in the primary disease, which was diagnosed as sprue. Fullerton and Innes [6] reported one case of steatorrhea with purpura and melena, but prothrombin times were not reported. Butt et al.[7] reported two cases with abnormal prothrombin times but without purpura, and Clark [8] and his group one similar case. Two patients in Colcher's [9] group of seven cases showed purpura, and five had hypoprothrombinemia. The standard texts, such as Wintrobe's *Hematology* [10] and Cecil's *Medicine*,[11] give only passing mention to the occurrence of purpura in sprue, and do not describe severe hypoprothrombinemia as a complication. Several other large studies demonstrate the rarity with which this situation arises. Stefanini in his monograph [1] describes 1,069 cases of sprue with five cases of purpura, all related to thrombocytopenia secondary to aplastic anemia. Adlersberg's [12] 40 cases included four patients with a bleeding tendency, with two deaths from hemorrhage, one with severe hepatic necrosis and one with a thrombocytopenia. No prothrombin times were given. The 100 cases described by Rodriguez-Molina [13] did not exhibit purpura. In summary, then, hypoprothrombinemia is a not infrequent complication of sprue, whereas frank bleeding and marked purpura occur rarely.[14]

The disordered physiology in sprue is believed to be due to an abnormal functional state of the wall of the intestine.[15] This results in a defective capacity to absorb many essential substances. Significantly, fats are poorly handled, with accompaning steatorrhea. This is associated with multiple deficiencies of the fat-soluble vitamins, in particular D, A and K.[16] The steatorrhea and tetany of sprue are well recognized as part of the syndrome, and the skin and visual findings of vitamin A deficiency are likewise familiar. There are a number of mechanisms which may account for the vitamin K deficiency.

First, a defect in absorbing fats prevents normal absorption of vitamin K, a fat-soluble vitamin. Second, it has been shown that vitamin K may be produced by the normal intestinal bacteria.[17] With the change in bowel contents and intestinal motility, normal K production may be defective. Hypermotility of the bowel, with diminution in the time for absorption, may be a third explanation, and poor intake a fourth possibility. Fifth, hepatic insufficiency may occur, with inadequate formation of prothrombin in the liver. In the case described, liver dysfunction was not evident and the dietary intake was quite adequate. The most important factor is very likely deficient absorption of the vitamin.

The sprue syndrome represents one particular situation in which a pathologic alimentary state may result in defective synthesis and absorption of vitamin K. Mackie [18] reported 71 cases of hypoprothrombinemia, of which 57 were not jaundiced. One case of sprue was included with a prothrombin time of 2 minutes. Twenty-eight of these cases were diagnosed as ulcerative colitis, and other conditions such as regional ileitis, bowel anastomoses and fistulae were included. Matoth [17] described 21 cases of infantile diarrhea in which 20 had elevated prothrombin times and in which it was felt that hypermotility and deficient formation of vitamin K in the bowel were the primary defects. Albright's case [16] of regional ileitis with multiple surgical resections presented an instance of multiple hypovitaminoses (fat-soluble), with vitamin K deficiency evidenced by purpura, gum bleeding and a prothrombin time of 13%. Potentially, then, diseases commonly associated with diarrhea may be accompanied by prothrombin deficiencies. Clinically, the implications of this problem are apparent with regard to substitutive therapy.

Purpura in sprue, as in other diarrheas producing hypoprothrombinemia, should be treated promptly with vitamin K. The most rapid results have been reported with K_1 intravenously. Maintenance therapy with oral vitamin K is satisfactory provided the vitamin is water-soluble. In the presence of frank bleeding immediate blood transfusions should be given. These measures of course apply only to one specific sprue deficiency. Dietary therapy as well as substitution of other vitamins is a basic requirement. The question of hormone treatment is not within the scope of this paper, but the patient described benefited substantially from cortisone.

Conclusions

A case of sprue is described which presented with extensive purpura and gastrointestinal bleeding of such severity as to constitute a medical emergency. This was found to be due to marked hypoprothrombinemia secondary to vitamin K deficiency. The importance of recognizing and properly treating this clinical problem is well documented by this case study. The mechanisms for the development of vitamin K deficiency in sprue are discussed. The association of

purpura with chronic diarrhea should suggest immediate prothrombin studies. Sprue must be considered in the subsequent diagnostic work-up of the patient.

SUMMARIO IN INTERLINGUA

Es reportate le caso de un patiente qui exhibiva sever purpura associate con chronic diarrhea. Le caso habeva essite tractate como problema intestinal functional, e le signification del purpura non esseva recognoscite usque le patiente deveniva criticamente malade con extense sanguination cutanee e gastro-intestinal. Al tempore del admission al hospital le patiente representava un problema urgente. Prompte studios hemorrhagic demonstrava un marcate deficientia prothrombinic e un marcatissime prolongation del tempore de coagulation. Vitamin K per via parenteral e transfusiones sanguinee esseva administrate con le effecto de un prompte cessation del sanguination e un retorno a valores normal in le tests de coagulation. Le patiente esseva mantenite sin difficultate additional per un therapia a vitamina K. Extense studios demonstrava que iste patiente habeva sprue non-tropic con resultante absorption inadequate de vitamina K.

Es sublineate le importantia de recognoscer purpura e deficientia prothrombinic in casos de diarrhea chronic proque tal casos pote involver serie problemas de malabsorption. Le appropriate therapia a reimplaciamento pote consister in le administration de vitamina K pro prevenir le disveloppamento de deficientias prothrombinic si tosto que iste situation es recognoscite. Le acute problema de sanguination massive e purpura in association con diarrhea prolongate debe esser diagnosticate promptemente. Therapia per transfusion sanguinee e vitamina K in administrationes parenteral es urgente. Illo servi rapidemente a corriger le disordine hemorrhagic.

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OBSERVATIONS ON A CASE OF MIXED PORPHYRIA WITH SPECIAL REFERENCE TO PATHOGENESIS AND TREATMENT *

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IT has recently been possible to study a young man with diabetes mellitus and mixed porphyria. This paper deals with observations concerning the clinical course, pathogenesis and therapeutics in the latter disease. The association of diabetes with porphyria has occasionally been noted [1] and seems most common in porphyria cutanea tarda,[2, 3] but so far as we are aware has not been previously described in mixed porphyria.

TABLE 1

The Classification of Porphyria, as Modified from Watson[4]

Types of Porphyria	Clinical Syndrome		Porphobilinogenuria	Tissue Containing Major Concentration of Porphyrins
	Abdominal and Neuropsychiatric Symptoms	Cutaneous Symptoms		
I. Porphyria erythropoietica (congenital porphyria)	0	+	0	Bone marrow
II. Porphyria hepatica				Liver
a. Acute intermittent porphyria	+	0	+	a. As precursors
b. Porphyria cutanea tarda	0	+	0	b. Preformed
c. Mixed porphyria	+	+	±	c. Preformed and/or as precursors

A brief review of the types and major features of porphyria, following Watson's classification, is helpful in any discussion of this disease and is presented in table 1.

Because of its unusual features our case is described in detail.

CASE REPORT

Because of severe periumbilical and left lower quadrant abdominal pain, obstipation, nausea and vomiting, a 31 year old carpenter of Italian descent was admitted

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From the Division of Medicine (Metabolic Section), Brooklyn Veterans Administration Hospital, Brooklyn, N. Y.

to the Metabolic Section of the Brooklyn Veterans Administration Hospital on December 6, 1953.

Since the development of classic symptoms of diabetes mellitus in 1945 he had used insulin (crystalline, protamine zinc and NPH) in doses ranging from 40 to 70 units daily. There had been no episodes of diabetic coma, although control had been poor.

In January, 1953, while en route by air from New York to California, the patient developed abdominal pain, vomiting and obstipation. He was hospitalized in California, where increased cutaneous pigmentation and "an elevated blood pressure and rapid pulse" were noted. Sigmoidoscopic examination demonstrated an "extrinsic obstruction" at the 8 inch level. At laparotomy, spasm was present in the sigmoid colon and the proximal bowel was distended. No organic lesion was found. A transverse colostomy was performed. Postoperatively, the patient complained of severe genital numbness and leg pain, but the abdominal symptoms disappeared. He was transferred to the Fresno Veterans Administration Hospital with the diagnoses of neurogenic bowel similar to megacolon but possibly due to diabetic neuropathy, possible cord tumor, possible hemochromatosis.

At the Fresno Veterans Administration Hospital the patient complained bitterly of numbness over the saddle area, dysesthesias of the trunk and generalized weakness. The blood pressure was 100/70 mm. of Hg; the pulse, 120 per minute. The knee jerks were absent, and there was a tremor of the outstretched hands. A sensory examination was normal. Laboratory examinations there revealed fasting blood sugars ranging from 30 to 250 mg. per 100 c.c., a serum cholesterol of 262 mg. per 100 c.c., a negative cephalin-cholesterol flocculation test, and a prothrombin time that was 90% of normal. There was 16% Bromsulphalein retention in 45 minutes. A liver biopsy showed "considerable yellowish pigment in rather large blebs . . . in the liver cells . . . and a slight increase in stroma with scattered lymphocytic infiltration." A determination of the basal metabolic rate was normal.

While at this hospital the patient experienced several minor and one severe (coma) insulin reactions, following which the weakness and numbness became more severe. There was no recurrence of porphyric abdominal distress. The colostomy was closed under spinal anesthesia and without untoward effect except for the appearance of severe calf cramps. He was considered to have an "inferiority complex" and an opiate "withdrawal-reaction." Liberal quantities of phenobarbital and Nembutal were prescribed. No beneficial effect was noted from vitamin B complex, multivitamin preparations or thiamine. The patient gradually regained strength and part of the 60 pounds which he had lost and was discharged on March 11, 1953.

Following his discharge from the Fresno Veterans Administration Hospital, and in temporal relation to sunbathing, "water blisters" developed on the face, neck and volar and dorsal aspects of both hands. He noted that new lesions appeared where he scratched, and that his hands bruised and his "knuckles skinned" with minor mechanical trauma. A dermatologist diagnosed epidermolysis bullosa. The cutaneous disturbance lessened and the patient returned to New York.

Between May and December, 1953, a number of minor episodes of abdominal pain, obstipation, nausea and vomiting occurred; each subsided in the space of one to three days. On Thanksgiving Day he imbibed liberally of beer, wine and whiskey and for the next fortnight the abdominal symptoms were continuous and became progressively more severe. He was admitted to the Brooklyn Veterans Administration Hospital on December 6; no flatus had been passed for three days, and repeated enemata had been unsuccessful.

The patient had noted occasional mild blurring of vision during the previous year. For three years there had been a tendency toward impotence, although he had impregnated his wife a few months prior to this hospitalization. There was no

past history of jaundice, edema or renal disease. On close questioning the patient's wife (who had been doing the urinary sugar analyses prior to admission) stated that her husband's urine had occasionally appeared dark and sometimes "orange" in color.

The family history is not adequate, and no members were available for examination. It was learned, however, that a sister, aged 45, has been troubled by blisters on her hands during the last several years.* Another sister, aged 26, had recently had a thyroidectomy. A brother had died of a "brain tumor" (no pathologic diagnosis) at the age of three. Three other brothers and the parents lack symptoms which significantly suggest porphyria hepatica. Diabetes mellitus is known to be present only in a maternal aunt.

Physical examination revealed a young white male who was moderately dehydrated and complained of severe abdominal distress. The blood pressure was 180/100 mm. of Hg; pulse, 100; temperature, normal. The skin showed diffuse brown pigmentation and was cool and moist. The pupils were miotic (opiates), and the fundi were normal; arteriolar attenuation was absent. The abdomen was soft, although slight left lower quadrant tenderness was present and bowel sounds were markedly diminished. The cecum and ascending colon were palpably distended. The abdominal scars were well healed. The liver was at the costal margin and the spleen was not palpable. Superficial pigmented irregular scarring was present on the hands, and extended to the wrists. Neurologic examination was negative.

Laboratory Data: The clinical diagnosis of porphyria was rapidly confirmed by the demonstration of porphobilinogenuria by the Watson-Schwartz test [5] and of intense red fluorescence in ultraviolet of an appropriately extracted aliquot of urine. Although the freshly voided urine was of normal color on admission, it darkened when acidified and heated.[6] It was unfortunately not possible to obtain more than occasional quantitative porphyrin urinalyses: an average of 35 mg. uroporphyrin and 6.8 mg. coproporphyrin was excreted daily. Isomeric analyses were not performed. The Watson-Schwartz reaction was persistently positive to an average dilution of 1:40, and was noted to be strongly positive in the complete absence of symptoms on several occasions.

The admission hemogram showed a white cell count of 11,400 per cubic millimeter, with 88% polys, 2% bands, 7% lymphocytes, 2% monocytes and 1% eosinophils. The hemoglobin was 14.1 gm. per 100 c.c., the hematocrit, 46%. The erythrocyte sedimentation rate (Wintrobe) was 7 mm. per hour. The blood urea nitrogen was 9; creatinine, 1.0; uric acid, 5.2; fasting blood sugar, 367 mg. per 100 c.c. A serum amylase measured 130 Somogyi units. Serum alkaline phosphatase was 12 King-Armstrong units; cephalin-cholesterol flocculation, 2 plus; thymol turbidity, 1.7 Maclagan units; bilirubin, 0.9 mg. per 100 c.c. Albumin measured 5 and globulin 2.3 gm. per 100 c.c. Cholesterol and cholesterol esters were 355 and 270 mg. per 100 c.c., respectively. A Bromsulphalein retention of 17.2% was noted in 45 minutes. Admission urinalyses showed normal concentrating ability, acid pH, no albumin, 0 to 4 plus sugar and no bile or abnormal sediment. Serum electrolytes were within normal limits. Stool guaiac tests were negative. An electrocardiogram and chest x-ray were within normal limits. Flat plate of the abdomen showed several segments of slightly dilated intestine.

Course: The patient's severe abdominal pain was controlled moderately well with Demerol and levorphan tartrate as required. Barbituric acid derivatives were strictly withheld. Intravenous alimentation was required for considerable periods of time, and repeated chemical determinations revealed no evidence of significant serum electrolyte alterations. The diabetes was cautiously controlled with crystalline and NPH insulins as indicated; neither hypoglycemia nor acidosis developed.

* The diagnosis of porphyria cutanea tarda has recently been confirmed in California by appropriate laboratory studies.

As will be commented upon below, the patient alternately demonstrated abdominal and neuropsychiatric symptomatology until the second week of February, 1954; thereafter he remained free of these symptoms. During the phase of acute porphyric symptoms many therapeutic agents were tried. Opiates and chloral hydrate were of distinct value. ACTH and cortisone appeared to help. No beneficial effect was noted with neostigmine, Regitine, Apresoline, Etamon, calcium gluconate, d-tubocurarine, Veralba, massive doses of vitamins, including B_{12}, and taurocholic acid.

A refractory left pyelonephritis, thought to be secondary to catheterization, developed on January 15, 1954 and the patient ran a febrile, toxic course until January 28. During the acute phase the urine showed 2 to 3 plus albuminuria and heavy pyuria, but in March and April only moderate pyuria persisted, pyelonephritic symptoms were absent, the patient felt well and was accordingly discharged on chemotherapy on April 23, to be followed in clinic.

From January 30 to February 25 massive edema appeared in association with hypoalbuminemia and anemia. Serum albumin was 2.3 gm. per 100 c.c. on January 26, and gradually increased to 4.7 gm. on February 25. The anemia was normochromic, with a minimal hemoglobin of 7.9 gm. per 100 c.c. and an average reticulocytosis of 3.8% (1.5 to 7.9%). A sternal bone marrow aspirate revealed no distinct abnormality, a Coombs' test was negative, and serum bilirubin remained within normal limits. No splenic enlargement could be detected. This picture was thought to be due to relative starvation, and with the aid of a markedly improved dietary intake and 1,000 c.c. of whole blood it completely cleared as the patient became free of the distressing porphyric abdominal symptoms, renal infection and albuminuria.

Following discharge the patient has been free of porphyric abdominal and/or neuropsychiatric symptoms. In May he passed a tissue plug from the left kidney and since that time has had neither albuminuria nor pyuria. In June, while otherwise asymptomatic, he developed mild epidermolysis bullosa, as he had in the spring of 1953. The diabetes is well controlled with 60 units of NPH insulin daily. The patient was strongly advised to avoid barbiturates, alcohol and hypoglycemia.

Discussion

1. *Interrelations of Hypertension and Abdominal and Neuropsychiatric Symptoms:* It has occasionally been observed that although hypertension coincides with the acute abdominal manifestations of porphyria, the neuropsychiatric symptoms are likely to occur when relative hypotension sets in and abdominal distress wanes.[7] The typical sequence as seen in the present case is illustrative of this phenomenon. Hypertension is noted to appear paroxysmally as abdominal pain and obstipation occur. At this time the abdomen is quiet and no neurologic abnormalities are present. Urinary retention may require the use of indwelling catheterization within a few days of the onset. After a variable period of time the blood pressure (especially the diastolic pressure) falls to normal or low levels, with concomitant remission of abdominal distress. At this time neuropsychiatric symptoms appear which, in our patient, consisted variously of a left ulnar numbness, generalized weakness and depressed deep tendon reflexes, blurred vision, "dizziness," disorientation and mildly psychotic behavior. On one occasion it was possible to predict correctly the onset of a typical porphyric abdominal attack by the prior detection of a paroxysmal blood pressure elevation.

2. *Inverse Relationship of Cutaneous and Abdominal-Neuropsychiatric Phases:* The observation has previously been made that in mixed porphyria an

inverse relationship may exist between the symptoms of porphyria cutanea tarda and those of acute intermittent porphyria.[6, 8] In the present case, active manifestations of porphyria cutanea tarda occurred on only two occasions, separated by a free period of one year, and in each case following by several months the syndrome of acute intermittent porphyria. In each case the cutaneous disturbance appeared in the spring. Schmid and colleagues reported one case of mixed porphyria in which it was observed that when cutaneous symptoms predominated large quantities of preformed porphyrin were present in the liver, as is the usual case in porphyria cutanea tarda, while when abdominal symptoms were predominant the hepatic porphyrin was primarily in the form of precursors, as is typical of the acute intermittent variety.[2]

The temporal and sequential relationship of clinical manifestations in this case of mixed porphyria is schematized in figure 1.

3. *Porphyria and Diabetes Mellitus:* That the diagnosis of porphyria may be overlooked in individuals with "diabetic neuropathy" is well illustrated by the present case. It is of interest that the cutaneous pigmentation, hepatic cirrhosis, diabetes and neuropathy also mimicked hemochromatosis. Sterling, Silver and

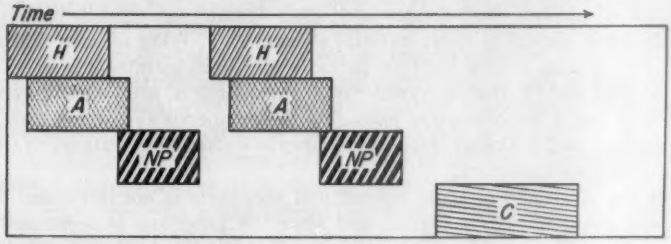

FIG. 1. Schematic representation of the temporal and sequential relationship of the clinical manifestations in the present case of mixed porphyria. (H = hypertension, A = abdominal syndrome, NP = neuropsychiatric syndrome, and C = cutaneous syndrome.)

Ricketts [1] noted the presence of diabetes mellitus in three * out of eight cases of porphyria studied by them. It is interesting that in their first case, which was initially diagnosed as "diabetic neuropathy," the appearance of neurologic porphyric symptoms was suggestively related to a hypoglycemic reaction, while in ours there was an apparent worsening of neurologic symptoms following an insulin reaction in January, 1953.

Only two out of 153 cases of porphyria reported by Schmid and associates [2] had a coincident diabetes, while only three of the elderly group of 17 patients studied by Brunsting et al.[3] were diabetic. From these data a significant coincidence of the two diseases cannot be adduced. In these series [2, 3] diabetes was noted only in association with the cutanea tarda variety of porphyria. To our knowledge, it has not previously been reported in association with mixed porphyria.

4. *Stress and Acute Porphyria:* It was interesting to observe in the present case that the stressful occasion of an acute renal infection coincided with a lysis of

* Although their first case is acceptable, the symptoms of the second and third cases quoted by these writers do not significantly suggest those of porphyria, and porphobilinogenuria could not be demonstrated in the third case.

porphyric symptoms. On January 12 to 14 the blood pressure averaged 170/110 mm. of Hg, and porphyric symptoms were moderately severe. Following the development of infection with fever and toxicity, starting on January 15 and reaching an apex on January 19 and 20, porphyric symptoms rapidly subsided and the blood pressure returned to normal levels. Fever and toxicity were absent after January 26, and on January 30 porphyric symptoms recurred. Although the evidence is tenuous at best, the relation is not dissimilar to that observed following ACTH administration.

Pathogenesis and Therapeutic Attempts in Porphyria Hepatica

In the past decade the diagnosis of the various porphyrias has been made with increasing frequency and dexterity. Concurrently, basic chemical delineation of the metabolic abnormalities has progressed, and the production of rather impressive experimental porphyrias in laboratory animals has been achieved. Despite these advances, however, convincing demonstration concerning the value of any but the most nonspecific forms of therapy has been lacking. In general, the management of acute intermittent porphyria has emphasized prophylaxis (avoidance of alcohol, barbiturates and other "toxic" agents which have been reasonably well shown to exert harmful effects [4, 6, 9]), relief of pain and apprehension (by opiates, chloral hydrate, paraldehyde), and maintenance of nutrition as well as fluid and electrolyte equilibrium. Avoidance of actinic and mechanical trauma is of major importance in managing the cutaneous symptoms, and hematologic support and judicious splenectomy are the outstanding features in the care of porphyria erythropoietica.

Since the syndrome of acute intermittent porphyria is not infrequently completely and spontaneously reversed, and since the prognosis is occasionally excellent, there is reason to be optimistic regarding the eventual demonstration of an effective therapy. The mechanism and pathogenesis of the porphyric syndromes remain obscure at the time of this writing. Some of the major knowledge and theory concerning this matter will be presented here, and notation will be made of some of the many therapeutic agents recommended by others and/or tried in the present case.

1. *Relationship of Porphyrins to Symptoms:* In his excellent comprehensive review, Schwartz [6] notes that the chemical aberration in porphyria lies not in the qualitative nature but in the quantitative excess of pyrrole compounds found in this disease. Eight or more porphyrins are demonstrable in human urine. Of these, only coproporphyrin and uroporphyrin have been identified and are fairly well known. Both may occur naturally in two isomeric forms. Waldenström's porphyrin is a zinc-complex whose constitution is not yet settled. Porphobilinogen and other precursors or chromogens have also been found. Hematoporphyrin is an artificial porphyrin. A considerable number of pyrrole compounds, many of which have not yet been identified, might be implicated in the pathogenesis of porphyric syndromes.

When hematoporphyrin-treated animals are exposed to light there results a syndrome of cutaneous alterations, tachycardia, hypertension and hyperpnea until shock and death supervene.[10] Several porphyrin materials have been shown to produce photosensitivity in animals, and spasm in isolated segments

of gut.[11] The order of pharmacologic potency as judged from these studies is roughly as follows: hematoporphyrin, uroporphyrin I, coproporphyrin I, protoporphyrin, coproporhyrin III and uroporphyrin III.[12]

A syndrome resembling acute intermittent porphyria has never been produced in man by the administration of pyrrole compounds. A cutaneous reaction following the injection of 200 mg. of hematoporphyrin was considered dissimilar to the skin changes of spontaneous porphyria cutanea tarda.[12] The intravenous administration of 5 mg. of coproporphyrin III produced no observable effect in another individual.[4] Others of the numerous and reasonably suspect pyrrole compounds and complexes have not been tested to our knowledge.

Other evidence may be adduced against the concept that porphyric symptoms are related to pyrrole compounds per se: (1) Some otherwise normal individuals may show marked idiopathic coproporphyrinuria.[4] (2) Patients with diseases other than porphyria may excrete large excesses of various porphyrins and even of porphobilinogen.[13] (3) The "pathognomonic" increased porphyrin excretion may be lacking in some cases of acute porphyria,[4, 14] and porphobilinogen may be absent.[2] (4) Although generally larger amounts of porphyrins are excreted in porphyria erythropoietica and porphyria cutanea tarda than in acute intermittent porphyria, the former syndromes do not, per se, include abdominal and neurospychiatric symptoms. Similarly, between attacks of acute porphyria large amounts of porphyrins and porphobilinogen may persist in the urine.

It is of course not impossible that some as yet unidentified or unsuspected pyrrole compound is what Watson [4] calls the "villain in the piece."

No therapeutic agent has been clearly shown to influence favorably the clinical syndrome of acute porphyria in relation to the excretion of porphyrin compounds. An alkaline ash diet with added sodium bicarbonate was ineffective in one case.[15] A vegetable-and-meat-free diet was employed in a case of porphyria cutanea tarda by Wells and Rimington to minimize exogenous pyrroles without effect on porphyrinuria; Aureomycin also failed to alter porphyrin excretion patterns by way of a change in intestinal flora.[16] Taurocholic acid has been recommended as an antagonist to the manufacture or activity of the presumed pyrrole villain, but no satisfactory data pertaining to its use are available. Taurocholic acid was briefly tried in our patient, but could not be tolerated orally due to the severe abdominal symptoms.

2. *Possible Implication of Respiratory Enzymes and Hepatic Function in Pathogenesis:* Porphyrins are of extreme physiologic importance, constituting as they do essential components of respiratory enzymes such as hemoglobin, myoglobin, catalase and cytochrome C. The liver normally contains large amounts of porphyrins, and in porphyria hepatica their concentration increases greatly.[2]

A relatively high incidence of liver disease is found in porphyria hepatica. Dean [8] noted that there was "often evidence of liver damage" in his cases, while Brunsting et al.[8] were much impressed by the high incidence of alcoholism (12 cases out of 17), exposure to hepatotoxins, and disturbed liver functions in their group of porphyria cutanea tarda. Abnormal liver chemistries have been observed frequently and clinical jaundice occasionally.[17, 18] In the 31 cases histologically studied by Schmid, Schwartz and Watson,[2] the diagnosis of cirrhosis or early cirrhosis was made on five occasions. The histologic demonstration of

"mild cirrhosis" or "hepatitis" in porphyria hepatica has been frequently accomplished,[18–20] as it was in the case presently reported. In a number of cases, including the present one, an abnormal collection of yellow or brown granules has been noted in the liver,[18, 19, 21, 22] usually in the absence of jaundice.

Conversely, Watson [4] and Watson and Larson [9] found that patients with liver disease *and without porphyria* also put out excessive amounts of urinary coproporphyrins, and in three cases false-positive reactions for porphobilinogenuria have been noted.[13]

Schmid and Schwartz [23] recently produced a syndrome in rabbits by means of allylisopropylacetylcarbamid (Sedormid) which is remarkably similar to acute porphyria and in which are observed a marked porphyrinuria (including Waldenström's porphyrin), porphobilinogenuria and hepatic alterations similar to those observed in human acute porphyria.[2] A striking and rapid decrease in liver catalase activity to one twentieth the initial levels was noted in their animals.[24] While no disturbance in hemoglobin or cytochrome C appeared, the possibility that respiratory enzymes other than catalase may have been disturbed has not yet been excluded.[6] It was postulated that the observed increases in pyrrole compounds is due to a block in their utilization in the synthesis of catalase, and that the symptomatology of hepatic porphyria is related to the enzyme deficiency. The deleterious effect exerted upon this disease by barbiturate and Sedormid in man strengthens this hypothesis, since theoretically they could competitively interfere with various prosthetic groups containing pyrimidine rings (viz., thiamine) and thus block the metabolic conversion of porphyrins to respiratory enzymes.[6]

Specific enzymatic disturbance has never been demonstrated in clinical porphyria. No other data are available by which it is possible to support the thesis that a defect in the activity of catalase or other respiratory enzymes is capable of producing symptoms and signs such as are seen in human porphyria. Furthermore, in the one pertinent study reported, Gray [14] found in a case of acute intermittent porphyria that hepatic catalase activity was normal, muscle cytochrome and myoglobin levels were high normal, and evidence of defects in hemoglobin metabolism was lacking.

In any case, a number of vitamins and vitamin preparations have been given variously for general support, to improve liver function and/or in the hope of enhancing the respiratory enzymes. Liver extract,[4, 19, 25, 26] vitamin B complex,[22, 25, 27] folic acid,[26, 28] nicotinamide,[27] riboflavin,[4, 16, 28] pantothenic acid [21, 22] and vitamin B_{12} [16, 28] have all been employed, and it is the consensus that significant benefit was not derived therefrom.

In the patient presented in this paper vitamin B complex, multivitamin preparations and thiamine were given in massive dosage without observable effect. Vitamin B_{12} was administered intramuscularly (1,000 micrograms every 12 hours) from January 8 to January 14 without discernible benefit.

3. *Implications of the Sympatheticotonic, Autonomic and Vascular Features of Porphyria:* The classic syndrome of acute porphyria includes such features as hypertension, dilated pupils, attenuation of retinal arterioles, tachycardia, restlessness, cold and clammy extremities, steady and/or colicky abdominal pain associated with intestinal spasm and loss of normal peristalsis, obstipation, urinary retention and cremasteric spasm.

The usual neuropsychiatric manifestations include motor weakness (sometimes patchy in distribution, sometimes in an ascending pattern), hyporeflexia, paresthesias and dysesthesias, psychoneurotic, psychotic and convulsive disorders and, rarely, objective sensory alterations. The neuropathologic findings have been generally nonspecific, and have variously consisted of alterations of the myelin sheaths and axons of peripheral nerves,[20, 29] degenerative and/or pigmentary changes in the sympathetic chain or autonomonic ganglia,[17, 20, 22, 30] retrograde degeneration in the thoracic intermediolateral column,[14] alterations in the anterior horn cells that are much more striking and common than changes in the posterior horn cells,[7, 14, 17, 20, 30] cerebral changes,[7, 29, 30] and abnormalities of various cranial nerves, including the vagus and hypoglossal.[29, 30] It has been pointed out in the literature that the neuropathologic findings are extremely variable and patchy,[7, 20, 29, 30] and Denny-Brown and Sciarra [7] consider the findings to result from a "widespread and patchy ischemia" produced by a humoral agent acting on blood vessels, a concept which at least has the advantage of being consistent with the sometimes rapid reversibility of the clinical process.

On the other hand, a more specific relationship of the central nervous system to porphyria is suggested by the increased porphyrin excretion [4] and the occasional porphobilinogenuria [18] which have been observed in poliomyelitis and other nervous system diseases, by the demonstration of fluorescing granules and coproporphyrin (2 to 3 gamma per 100 gm. white matter) in the normal central nervous system,[4] and by Gray's report [14] of an observed decrease of these fluorescing granules in a case of porphyria. Schmid, Schwartz and Watson,[2] however, found apparently normal fluorescence and coproporphyrin concentration of nervous tissue in one case of porphyria, even though no fluorescence could be demonstrated in the nervous tissue of a second patient. It seems clear that, although nervous system alteration may in some way be due to porphyria, the neuropathologic alterations are, per se, capable of producing in turn more, or less, distinct symptoms.

In accord with the vascular theory of pathogenesis of porphyric symptoms, Berg [18] and, more recently, Wells and Rimington [16] have implicated the capillaries as the shock organ. In acute porphyria it has been observed with capillary microscopy that these structures are reduced in number, that stasis is present, and that occasional aneurysmal dilatations are evident. These alterations were reversible with the administration of neostigmine plus Mecholyl, and the concept of capillary spasm possibly due to a defect in acetylcholine activity was suggested.[18] In a case of porphyria cutanea tarda without abdominal or nervous manifestations it was noted on biopsy of a skin lesion that there was thickening and "damage" to capillary walls in the upper corium, associated with intense polysaccharide staining of the basement membrane.[16]

The data presented above suggest that autonomic drugs, ganglionic blocking agents, and vascular and muscle relaxants deserve a trial in the symptomatic therapy of acute porphyria. A wide variety of such agents has been used.

Atropine has been employed for the relief of abdominal symptoms without success by several workers,[18, 19] and the writer has personally seen it used with similar failure. It has been observed that the spasm produced in isolated smooth muscle by porphyrin compounds is not reversed by atropine.[11]

Another parasympatholytic agent, *Trasentin,* has been used in acute porphyria, with the observation that it may have worsened abdominal pain and was of no value.[16]

Gordin [21] used neostigmine and felt that it helped counteract sympatheticotonia. Berg [18] observed temporary symptomatic relief of abdominal symptoms associated with increased bowel sounds and reversion of capillary microscopic findings to normal when he employed *neostigmine* and *Mecholyl;* he warned, however, that these agents may be dangerous. Others [22] found neostigmine of no value for abdominal symptoms. In a case with myasthenic but without abdominal complaints this agent was used with clear-cut benefit,[32] while in a similar patient it was unsuccessful.[33]

In the patient presented in this paper, 0.5 mg. neostigmine intramuscularly effected a slight increase in bowel sounds, no change in blood pressure and no appreciable relief of abdominal pain at the height of an abdominal crisis.

Intravenous *epinephrine* has been reported in one case [19] perhaps to worsen symptoms.

Priscoline, an adrenolytic and parasympatholytic drug, provided transient relief in one attack, while the adrenolytic *Benzodioxane* was ineffective in a more severe crisis in Wehrmacher's case.[19]

In dosage from 100 to 450 mg., *Etamon* (tetraethylammonium chloride) was administered intravenously on a number of occasions to Wehrmacher's patient,[19] with relief of abdominal symptoms for several hours. Repeated injections appeared to break up the "cycle" of abdominal pain when this mode of therapy was instituted within the first day or two of symptoms. In an especially severe crisis, Etamon was administered some three days after the onset of symptoms and was ineffective. In Schwartz's paper [6] it is stated without documentation that this agent appeared to be of value in the control of abdominal pain, but the notation is made that it may be dangerous.

In our patient, Etamon was administered intravenously at the height of an acute crisis on December 9. Fifty milligrams were instilled over a one minute period, with an abrupt fall in blood pressure from 160/102 to 126/90 mm. of Hg but without significant pain relief. Five minutes later the blood pressure had returned to 160/102 mm. of Hg, and another 70 mg. of Etamon were given, without clinical benefit despite our obtaining a minimal blood pressure of 110/70 mm. of Hg. Seven minutes after the second injection the blood pressure was 142/98 mm. of Hg, and 17 mg. of the same agent were rapidly injected over a one-second period, again without clinical benefit. A slow infusion of 250 mg. of Etamon was then given, again without definite benefit. Despite the administration of a total dose of 387 mg. of Etamon within a one hour period, the clinical status remained essentially unchanged except for maintenance of a more normal blood pressure for the next two days. The depressed bowel sounds were further diminished by the drug.

Three days later, on December 12, the patient became spontaneously free of abdominal distress and bowel sounds became normal. On December 14 he noted left ulnar numbness, and the blood pressure was observed to have fallen to 114/68 mm. of Hg. These symptoms cleared by December 16. On the evening of that day mild steady abdominal pain appeared and increased progressively. Within 24 hours of the onset of this attack 425 mg. of Etamon were administered

intravenously, again without effect upon pain and in association with diminution of bowel sounds.

Because of the hypertension and coincident clinical features demonstrated by our patient, a therapeutic test was made with several agents which to our knowledge have not previously been employed in acute porphyria. Neither phentolamine methanesulfonate (Regitine), hydralazine hydrochloride (Apresoline), nor a veratrum alkaloid (Veralba) was of value.

On December 8, while the patient's abdominal pain was severe and the basal blood pressure 180/100 mm. of Hg, 5 mg. of *Regitine* were administered intravenously. The maximal blood pressure response was noted one minute later when the reading was 156/84 mm. of Hg. Two minutes following the injection the initial blood pressure had been reverted to. There was no significant alteration of abdominal pain, and the blood pressure response was not indicative of excessive circulating adrenergic material.

During the same attack, 40 mg. of *Apresoline* were administered by rapid intravenous injection. No clinical benefit or pain relief was derived. The blood pressure and pulse were recorded at 180/100 mm. of Hg and 96, respectively, prior to injection. Following injection the pressure fell to a plateau of 120/60 mm. of Hg in 12 minutes, while the pulse rose to a plateau of 136. Hypertension returned an hour later.

Veralba was administered on the evening of December 19 for an attack which had commenced on December 16 and had progressed despite a trial of Etamon, calcium gluconate and curarization. The blood pressure was 160/102 mm. of Hg and the pulse 120 when an injection of Veralba (0.1 mg. in 10 c.c. diluent) was started intravenously at a rate of 0.5 c.c. per minute. The hypotensive response commenced after 5 c.c. had been given, and a minimal pressure of 110/70 mm. of Hg, associated with a pulse of 96, appeared a few minutes after the injection had been completed. The patient noted that his pain increased in relation to the Veralba effect, and he complained of slight nausea. The clinical status was still unimproved on the following day.

In his case [19] Wehrmacher reported immediate and complete relief of pain following curarization early in the course of an abdominal crisis; in a severe attack, where delayed treatment was instituted, tubocurarine chloride provided ineffective transient relief, and a *posterior splanchnic block* with procaine was effected, with immediate relief lasting for 24 hours. Splanchnic block was not reported by others, nor was it employed in the present case.

On the evening of December 17 our patient was curarized * with the intravenous administration of 60 units *d-tubocurarine*. Pain and Demerol requirements were in no wise affected. The potential danger of curarization in acute porphyria is obvious.

Related to the therapeutic attempts presented above is a single report [18] in which intravenous *procaine* was employed. It was observed in one case of acute porphyria that recurrent attacks could be abolished for at least 24 hours following infusion of 400 c.c. of 0.1% procaine solutions. The possible mechanisms involved in procaine remission are numerous.

Glyceryl trinitrate has been reported [19] ineffective in acute porphyria, and the present author has seen it employed without success on several occasions.

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4. *Endocrine Relationships:* Although the signs and symptoms of porphyria hepatica may occasionally suggest various endocrinopathies, corroborative data are lacking.[6] Adrenal cortical insufficiency has been suspected on occasion because of cutaneous pigmentation, weakness and abdominal crises, but the syndrome has been incomplete. Although hyponatremia has been observed in acute porphyria, neither symptoms nor electrolytes have been corrected by DCA.[21, 27] The relationship of porphyria to diabetes has been commented upon above.

That an indistinct relationship may exist between menses, pregnancy, parturition and acute porphyria has been suspected not infrequently.[4, 6, 12] It is well known clinically that an acute attack may coincide with the menses, although no specific mechanism has been demonstrated. It has been occasionally noted that whereas an exacerbation of porphyria may occur in the first trimester, a remission follows thereafter.[34] It has also been observed [4] that abdominal attacks may be related to parturition and the immediate postpartum period. The possibility that these phenomena may in part be ascribed to nonspecific effects of endogenous ACTH and steroid hormones and to their withdrawal can only be mentioned.

As was to be expected from their recent widespread use, ACTH and cortisone have been employed in a number of cases of porphyria hepatica. Janoff et al.[35] obtained a "dramatic remission" in a case of mixed porphyria within 12 to 24 hours. Watson reports that three acute cases out of six responded very favorably,[4] and Goldberg and co-workers noted improvement in one case.[27] Dean [8] also reports the apparent value of ACTH. Others failed to obtain clinical benefit in acute porphyria with cortisone [22] or ACTH.[36] It is of possible significance that cases exhibiting chronic neurologic disease were not benefited,[4, 36] while the majority of patients with acute manifestations were helped. Following ACTH administration, no alteration of porphyrin excretion was noted in several cases,[27, 36] while in one case [4] uroporphyrinuria markedly diminished, although coproporphyrin and porphobilinogen excretion were unchanged.

In the present case ACTH and cortisone were employed and appeared to be of value. On December 20 the patient was still having severe pain, and oral alimentation was impossible. Flatus was absent and a urethral catheter necessary for urinary retention. That afternoon a continuous infusion of 40 units ACTH per liter was initiated, each bottle being run over approximately an eight hour period. Within 24 hours the pain was moderately diminished, and within 30 hours flatus and urine were being passed spontaneously. Within 48 hours pain was minimal and opiates were no longer required. The patient was eating well and retaining all feedings at this time, and the infusions were discontinued and oral cortisone was substituted for the ACTH.

The blood pressure gradually fell from 154/100 mm. of Hg on December 20 to 116/80 mm. of Hg on December 23. The cortisone was gradually tapered and was discontinued on December 30 while the patient was still asymptomatic. Coincident with terminating cortisone therapy the patient complained of weakness and blurred vision. His blood pressure was 110/70 mm. of Hg and his reflexes were markedly depressed.

Within the next week mild abdominal pain associated with nausea and vomiting and urinary retention had recurred, and elevated blood pressures were again present. Accordingly, intravenous ACTH was reinstituted on January 15, and although the patient noted a decrease in pain he became confused as to time and

place on January 17. The ACTH was promptly discontinued and was followed within a day by sepsis due to a previously quiescent left pyelonephritis. As previously noted in this paper, a remission in porphyric symptoms occurred at this time and appeared related to the stress of sepsis (rather than to the short antecedent course of ACTH). In any case, with subsidence of the pyelonephritic toxicity, porphyric symptoms recurred. This feature is somewhat reminiscent of postpartum porphyric exacerbations and the recurrence of symptoms (rebound) after termination of the first course of ACTH and cortisone in the present patient.

5. *Psychiatric Factors:* It is classic that acute porphyria frequently mimics and is misdiagnosed as hysteria or psychoneurosis until the proper diagnosis is considered and confirmed. Olmstead [37] stresses that a hysterical personality is present even between attacks and that the basic personality is inadequate. In the interesting study of Visher and Aldrich [38] it was observed that the clinical picture was intensified following psychic trauma and improved with psychotherapy. In their case a complete clinical remission, associated with a disappearance of excessive coproporphyrinuria (but no change in excretion of uroporphyrin or porphobilinogen), has persisted for the three years of observation and psychotherapy. The same authors note briefly that a second case responded similarly well to psychotherapy.

Although these observations are unconfirmed, they are perhaps as impressive as any other therapeutic reports.

6. *Miscellaneous Therapeutic Agents:* a. *Zinc.* Variable amounts of the urinary porphyrins are excreted as a zinc-porphyrin complex in porphyria hepatica. It has been suggested that porphyric symptoms in this disease may be due to depletion of the body's zinc stores and, contrarily, that the complex of porphyrins may protect against symptoms. The former hypothesis is not supported by the normal hepatic and pancreatic concentration of zinc in Nesbitt's case.[25] The latter theory is inconsistent with the fact that symptoms of porphyria hepatica may be present in the complete absence of free porphyrins in the urine. Gilbert et al. fed zinc sulfate to their acute porphyric without clinical benefit.[22]

b. *Calcium gluconate.* The use of calcium was suggested by Mason, Courville and Ziskind [30] in 1933 for rather unconvincing theoretic reasons. It has been frequently employed, without success.[4, 15, 18, 19, 25, 27]

In the present case 10 c.c. of 10% calcium gluconate were administered intravenously, without apparent effect.

c. *Other agents.* Antihistaminics,[27, 39] magnesium sulfate,[19] cobra venom,[15] dimercaprol (BAL) [8] and a number of other agents have been occasionally and empirically employed in acute porphyria, without appreciable beneficial effect.

Comment

As may be deduced from the preceding review of the literature and discussion, and as is not unexpected in light of the clinical vagaries of porphyria hepatica, no single theory of pathogenesis and no mode of specific therapy in this disease can be considered satisfactory. Pathogenetic theories occasionally hint at basic mechanisms, but at the time of this writing none has successfully met the difficulties involved in clinical proof. A therapeutic armamentarium has

been developed, but no agent has shown itself to be of convincing, reproducible or specific value.

Summary

A case of mixed porphyria occurring in association with diabetes mellitus is reported. It is felt that no significant relationship exists between the two diseases.

In mixed porphyria an inverse relationship apparently exists between the syndromes of acute intermittent and cutaneous porphyria. During the acute phase, hypertension and abdominal symptoms and neuropsychiatric phenomena appear to be sequentially related.

Theories of pathogenesis and possible mechanisms in porphyria hepatica are reviewed. None is entirely adequate.

Specific therapeutics are lacking for porphyria; the symptomatic treatment of the disease is reviewed. Opiates and chloral hydrate were distinctly useful. ACTH appears to be of value in the acute abdominal and "sympatheticotonic" phase. As employed in this case, Etamon, Veralba, Regitine, Apresoline, neostigmine, calcium gluconate, curarization and vitamins were of no clinical or symptomatic value.

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Summario in Interlingua

Es describite le caso de un juvene adulto mascule in qui porphyria mixte appareva octo annos post le declaration de diabete mellite. Ben que il existe indicios de valor suggestive in supporto del conception que reactiones de insulina exacerba symptomas porphyric, nulle relation fundamental es demonstrabile inter diabete per se e porphyria.

Esseva notate que in le curso de attaccos de porphyria, hypertension, symptomas abdominal, e phenomenos neuropsychiatric se manifestava sequentialmente. Le syndrome cutanee variava inversemente con le manifestationes acute de porphyria.

In despecto del grande volumine de recerca in re le mechanismos de porphyria, nulle del theorias del pathogenese de iste morbo es adequate ab le puncto de vista theoric o ab le puncto de vista clinic. Le base del tractamento clinic es ancora prophylaxe (specialmente le evitation de barbituratos e alcohol) e un judiciose therapia supportative. Le base del diagnose es ancora "un alte grado de suspicion."

In le caso hic reportate, un numero de agentes therapeutic (includente alicunes non previemente investigate in iste connexion) esseva empleate pro le syndrome acute. Hydrato de chloral e opiatos esseva distinctemente de valor. Nulle valor clinic esseva notate in neostigmina, chlorido de tetraethylammonium, hydrochlorido de hydralazina, phentolamino, methanesulfonato, un alcaloide de veratrum, gluconato de calcium, vitaminas (includente vitamina B_{12}), e d-tubocurarina. ACTH e cortisona esseva apparentemente utile. Etiam le stress de un acute pyelonephritis pareva exercer un effecto benefic super le symptomas porphyric.

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THE USE OF L-ARTERENOL IN A CASE OF HYPERSENSITIVITY TO TETANUS ANTITOXIN *

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THIS is a report of an untoward reaction to horse serum (tetanus antitoxin) and its successful treatment with l-arterenol. Tuft [1] estimated that death from atopic reaction results once in 70,000 persons receiving injections of tetanus antitoxin. If reported incidence is a reliable index, clinical sensitivity to horse serum is comparatively rare. However, as with other unfortunate therapeutic reactions, the actual occurrence is greater than that reported.

Based on Feinberg's [2] classification of allergy to injected substances, we feel our patient's response was that of an immediate serum reaction. The patient gave a history of having previously received a sensitizing injection of horse serum. There was also a family history of atopy. Such reactions may occur within a few minutes up to several hours after an injection. Usually suffusion of the face, pruritus, angioneurotic edema, rhinitis, and sometimes tightness of the chest and asthmatic wheezing occur. If sensitivity is sufficiently great, or if a large amount of serum is injected, symptoms are likely to be more violent and limited to a shock state.

During the acute allergic attack one must still depend primarily on symptomatic treatment as indicated by the individual presenting clinical problem. In recent years the antihistamines, corticosteroids and corticotropins have been added to the classic armamentarium. Until recently, epinephrine alone has been most effective in partially combating the shock state accompanying allergic reactions. It is felt that this limited success of epinephrine is largely attributable to the fact that U.S.P. epinephrine contains varying amounts of l-arterenol (up

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to 36%).[3] The clinical success of l-arterenol in the treatment of shock due to a variety of causes, medical as well as surgical, prompted us to use it in treating the shock associated with the reaction in this patient.

Case Report

A 30 year old white male was admitted six hours after having sustained a scalp laceration. Prior to hospitalization the wound was sutured. The patient was then tested intradermally for sensitivity to horse serum and (apparently after a negative reaction) was given 1,500 units of tetanus antitoxin. About one-half hour later he experienced generalized malaise and within one hour noticed swelling of the lips, suffusion of the face, and a generalized erythematous rash accompanied by itching. The physician prescribed an antihistaminic preparation. Soon after this the patient

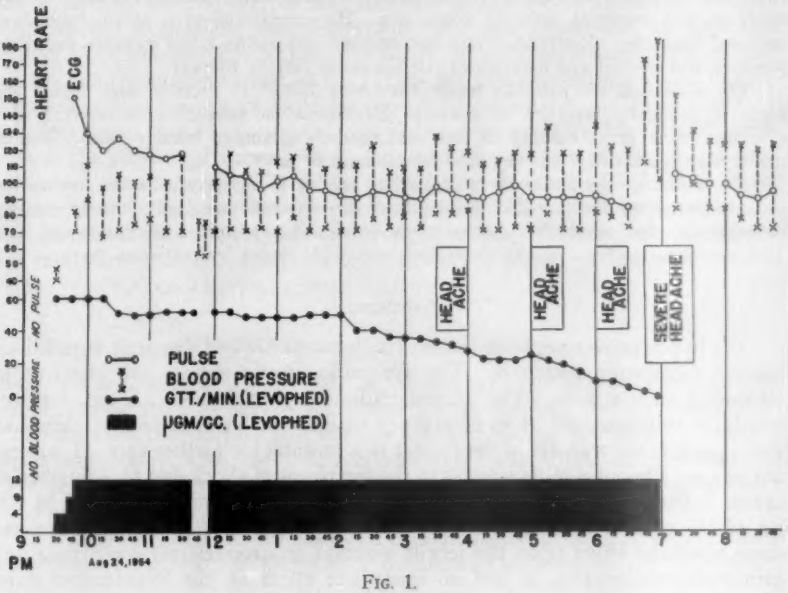

Fig. 1.

experienced severe abdominal cramps followed by repeated emesis and weakness. Three hours from the time of administration of tetanus antitoxin he developed chills and fever. He was then hospitalized. On admission he appeared acutely ill and somewhat restless, and complained of nausea and dizziness. The temperature was 103.2° F., the pulse and blood pressure were unobtainable, and the apical rate was 136. The lungs were clear throughout. The skin was covered by multiform macular erythematous areas admixed with crops of urticarial wheals. There was also a recently sutured laceration over the left frontal area.

Because of the absent blood pressure and pulse, l-arterenol (Levophed) was started intravenously at 9:30 p.m. Simultaneously, another infusion containing 25 mg. of ACTH in 500 c.c. of 5% glucose in water was given in the other arm.

L-arterenol was begun at a conservative concentration of 4 micrograms/c.c. (one ampule of 4 mg. in 1 liter of 5% glucose in water) at 60 drops/min. The concen-

tration was quickly and successively increased at 10 minute intervals until the desired pressor effect was obtained. This response was finally achieved with 12 micrograms/c.c. at 60 drops/minute.

From the graph one sees that at 9:50 p.m. the blood pressure had risen from 0 to 82/70 and at 10:05 p.m. to 110/90 mm. of Hg. At 11:40 p.m. the infusion infiltrated and the pressure promptly dropped to 74/60 mm. of Hg, even though the ACTH continued to flow into the other arm. Following re-insertion of the needle the pressure promptly returned to previous normotensive levels. Subsequently, a progressively slower rate of administration was sufficient to maintain the pressure. The rate was gradually reduced so that, after nine hours, the patient was receiving only 16 drops/min. and yet his pressure was 132/80 mm. of Hg. After five and one-half hours of therapy he became intermittently restless and complained of a severe, throbbing headache whenever the systolic blood pressure exceeded 120 mm. of Hg. After nine hours of therapy the blood pressure rose quickly to 180/100 mm. of Hg while he was receiving only 12 drops/min. He complained of a severe, pounding occipital headache. L-arterenol was discontinued and within a few minutes the blood pressure was normal and maintained itself without further therapy.

On admission the patient's temperature was 103.2° F. rectally, and during the night it gradually returned to normal. Urinalysis on admission revealed 3 plus albumin and a great number of fine and coarsely granular tubular casts. Repeat urinalysis the next day was negative for albumin or casts.

On discharge the patient was advised to see his family physician for medication in anticipation of the possible development of serum sickness. Follow-up inquiry revealed that one week after discharge he developed swelling of his hands and lips. This complication was readily controlled within 24 hours by cortisone therapy.

Discussion

The hypotensive state is an immediate threat to life and demands expeditious specific therapeutic measures. The sympathomimetic amines are effective in combating such a state. The administration of phenylephrine, 5 mg. intravenously, is recommended as an emergency measure in the treatment of shocklike states prior to the transfer of the patient to a hospital for further care. L-arterenol was used because of its success in the treatment of shock due to a number of causes. The patient under discussion was also given 25 mg. of ACTH in 500 c.c. of 5% glucose in water concurrently. Although the ACTH may have had some beneficial effect upon the febrile reaction, gastrointestinal complaints and urticarial manifestation, it had no immediate effect on the hypotensive state. This was clearly illustrated by the fact that, when the l-arterenol infusion began to infiltrate, the blood pressure dropped from 118/70 to 76/56 mm. of Hg in spite of the fact that the infusion of ACTH was continuing in the other arm.

The dose of l-arterenol to be used cannot be standardized, nor does it remain the same throughout the course of therapy. The usual initial concentration of l-arterenol employed is one containing 4 micrograms/c.c. The ideal therapeutic goal is to attain an adequate concentration of the drug in the shortest period of time. This can be readily attained because the pressor effect is almost immediate. By taking blood pressure readings at frequent intervals, one can decide within a five to 10 minute period whether the desired pressor effect has been attained. Inactivation of l-arterenol is rapid, and one is not faced with the problem of cumulative effect; therefore, the concentration was rapidly increased until a pressor effect was had. Thus, with the use of such a biophysiologic titration method, the

concentration of l-arterenol in the infusion was quickly increased in three 10-minute intervals to 12 micrograms/c.c. During this titration the rate was maintained at 60 drops per minute. In the subsequent eight hours the rate of infusion was gradually decreased to 12 drops per minute. In retrospect, at this stage it would have been advisable to dilute the concentration of l-arterenol in a stepwise manner in order to maintain a more practical rate of flow. After five and one-half hours of administration of the infusion the patient began to complain of intermittent headache of variable severity whenever the systolic blood pressure exceeded 120 mm. of Hg. It has been reported [5] that l-arterenol causes an increase in cerebrovascular resistance and a decrease in cerebral blood flow. It is quite possible the headaches were due to these physiologic effects.

After nine hours of therapy the patient complained of an excruciating occipital headache, and by that time his blood pressure had risen abruptly from 120/70 to 170/110 and then to 180/100 mm. of Hg within 15 and 30 minutes, respectively. L-arterenol was discontinued and this resulted in an immediate drop of blood pressure to normotensive levels, with complete subsidence of headache. The potentiating effect of ACTH on the pressor response to an intravenous infusion of l-arterenol has been reported by Kurland and Freedberg.[6] It is believed that this rather sudden rise in blood pressure associated with headache, in the absence of a change in the concentration or rate of administration of l-arterenol, may have been due to the potentiating effect of ACTH administered intravenously. The fact that such an effect occurred only after nine hours of continuous intravenous ACTH therapy strongly suggests that in this patient, who was in a state of severe vasomotor collapse, such a period of time was required for the resumption of normal adrenal function.

Summary and Conclusions

A case is described of immediate serum reaction with severe vasomotor collapse following the administration of tetanus antitoxin.

L-arterenol was utilized as a pressor agent to combat the severe protracted hypotensive state. The proper dose of l-arterenol was arrived at by means of a rapid progressive increase in concentration of the drug, controlled by frequent blood pressure readings.

It is suggested that the simultaneous continuous use of ACTH intravenously had a potentiating effect on the pressor response of l-arterenol.

Summario in Interlingua

Es reportate un caso de immediate reaction seral post injection de antitoxina a tetano. Le sensibilitate del patiente esseva sufficientemente pronunciate pro describer le al tempore del presentation como un individuo in stato de profunde collapso vasomotor. Viste que le tractamento de reactiones allergic es extensemente un tractamento symptomatic e viste que l-arterenol ha essite usate con successo in casos de choc, ille amino sympathomimetic esseva administrate intravenosemente. Al mesme tempore un secunde infusion de ACTH esseva comenciate. Le concentration de l-arterenol esseva rapidemente augmentate usque le desirate effecto pressoral esseva obtenite. Un reduction del pression sanguinee sequeva le infiltration de l-arterenol in despecto del mantenentia del fluxo de ACTH. Isto demonstrava le carentia de effecto immediate de ACTH super le stato hypotensive. Plus tarde, quando le quan-

titate de l-arterenol requirite pro le mantenentia del pression sanguinee esseva reducite, un subitanee episodio de hypertension se manifestava, accompaniate de hypertensive encephalopathia. Nos opina que iste episodio esseva le resultato del effecto potentiante de ACTH super le responsa pressoral de l-arterenol, e que le intervallo ab le initiation del therapia usque al declaration de ille episodio esseva le tempore requirite ante que le ACTH poteva stimular le resumption de normal functiones adrenal.

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ECTOPIC PREGNANCY MASQUERADING AS AN ACUTE HEMOLYTIC CRISIS *

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It is almost a medical truism that ruptured ectopic pregnancies are clinically capricious, and therefore this diagnosis must always be kept in mind in the evaluation of abdominal symptoms in any female of childbearing age.[1, 2] The knowledge that acute hemolytic crises may clinically resemble surgical abdominal emergencies of various types has been repeatedly emphasized in the past several decades.[3, 4, 5, 6] No previous case report has been found of a patient with tubal rupture who was initially thought to be suffering an acute hemolytic crisis. For this reason a case is presented whose clinical picture seemed entirely consistent with a hemolytic crisis but who was subsequently found to have sustained a difficult to interview.

Case Report

The patient, a 33 year old Negro female who works as a domestic, was referred into the hospital by her family physician with a diagnosis of possible peritonitis. She had been ill for about seven days, and on admission was very apprehensive and difficult to interview.

One week before admission her usual state of excellent health terminated. She began to suffer nausea, vomiting, abdominal pain and distention, and constipation requiring enemas. Her pain was chiefly in her midepigastrium, radiating down the midline of the abdomen and across both costal margins. She also noted severe shoulder pain in the region of her right acromion. During her period of heaviest vomiting several days before admission her urine had seemed unusually dark; no

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change in the color of the eyes or of the stools had been noted. For several days prior to admission she had had no nausea or vomiting, but her gaseousness and bloating had increased and just before admission her abdominal pain became severe.

Past medical history was pertinent only for four uneventful pregnancies. Her menses, always regular, had begun on schedule the day of admission. There were no missed periods. All drug ingestion was denied. No food intolerance had ever been noted before the present illness. The patient had never been told that she was anemic.

Physical examination on admission revealed a well nourished young Negro female appearing apprehensive and acutely ill. Her temperature was 100.2° F. (per os); pulse rate, 90; blood pressure, 120/80 mm. of Hg. Abnormal physical findings were limited to the abdomen. There were moderate distention and diffuse tenderness, most marked in both upper quadrants. The left upper quadrant appeared more tender than the right, but fist percussion was more painful over the right costal margin. No masses or organs were felt, but tenderness prevented deep palpation. There was no costovertebral angle tenderness. Muscle rigidity was marked but seemed predominantly voluntary and most pronounced in the upper abdominal quadrants. Bowel sounds were present and physiologic. One examiner thought he could elicit a fluid wave and another examiner believed he could demonstrate shifting dullness, but both these findings were disputed. Pelvic examination revealed a firm, healthy appearing cervix with a small amount of fresh blood in the cervical os. The uterus was within normal limits of size and consistency, and there were no adnexal masses or tenderness. There was one painful external hemorrhoid. Brown feces, guaiac negative, were obtained on the examining glove.

Initial laboratory data included: white blood cells, 20,400 per cu. mm., with 65% mature polymorphonuclears and 20% bands; hemoglobin, 5.2 gm. No sickling of erythrocytes was observed. The next day the hemoglobin was 4.6 gm.; there were 26% reticulocytes, with marked anisocytosis and poikilocytosis, and 5 nucleated erythrocytes per cu. mm. Urine urobilinogen was positive through a dilution of 1:400; there was no urine bile. Serum bilirubin totaled 2.2 mg. per 100 c.c., of which 0.51 mg. was direct reacting. There was no plasma methemoglobin; methemalbumin was present. Cold agglutinins and direct and indirect Coombs' tests were negative.

Twenty-four hours after admission and therapy with penicillin and streptomycin, the patient's temperature had fallen to normal and her abdominal pain, tenderness and rigidity had disappeared. By this time the admitting impression of acute cholecystitis had been changed to an acute hemolytic crisis of undetermined etiology.

Two days after admission a serum Friedman test performed on blood drawn the first day was reported as positive. Gynecologic consultation was obtained and the pelvic findings reported above were confirmed. However, needle colpotomy was performed and dark, grossly bloody fluid which did not clot was aspirated from the peritoneal cavity. The patient was promptly transfused and a laparotomy performed. The peritoneal cavity contained approximately 2,000 c.c. of dark blood. The right fallopian tube was swollen and hemorrhagic on its external surface. After removal its lumen was found to contain a bulbous mass 3 by 3.8 by 1.5 cm. which was histologically placental tissue. Postoperative convalescence was uncomplicated; the patient was discharged nine days after admission.

Summary

It has been said regarding patients with ectopic pregnancy that "the factor most typical of these patients is their atypical clinical picture." [1] A case of ruptured tubal pregnancy which was initially misdiagnosed as an acute hemolytic crisis is presented.

SUMMARIO IN INTERLINGUA

Es ben cognoscite que pregnantias ectopic rupturate recipe frequentemente misdiagnoses initial. Assi le possibilitate de tal pregnantias debe esser prendite in consideration in le evalutation de symptomas abdominal in omne femininas de etate impregnabile. In le curso del passate decennios on ha signalate repetitemente que acute crises hemolytic pote resimilar syndromes abdominal de urgentia chirurgic.

Es presentate un caso de ruptura tubal, interpretate initialmente como acute crise hemolytic. Le patiente, 33 annos de etate, habeva omittite nulle menstruation. Signos e symptomas de dolor e sensibilitate abdominal esseva transiente. Le constatationes laboratorial includeva un anemia de 5,2 g de hemoglobina. Esseva constatate 26 pro cento de reticulocytos e 5 erythrocytos nucleate per millimetro cubic. Urobilinogeno de urina esseva augmentate; esseva presente hyperbilirubinemia de 2,2 mg per 100 cm ^{3}.

Il seque que rupturate pregnantia ectopic debe esser prendite in consideration in le diagnose differential de acute crise hemolytic.

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THE TREATMENT OF REFRACTORY ANEMIA WITH COBALT *†

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SINCE Waltner and Waltner [1] first discovered that cobalt produces polycythemia in animals, physicians have attempted to employ this element in the therapy of anemia. One group of anemias that has attracted particular attention is that of the refractory anemias. Most investigators have found cobalt to have no therapeutic value in this type of anemia. Berk, Burchenal and Castle [2] treated five patients with refractory anemia and hypercellular marrow with 300 mg. of cobaltous chloride daily with no reticulocyte response or rise in blood values. Weissbecker [3] found cobalt to be of no value in six cases of aplastic anemia.

However, a few favorable reports are available. Seaman and Koler [4] described one case of refractory anemia with erythrocytic hypoplasia of the bone marrow of five years' duration that recovered 64 days after beginning oral

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† Cobaltous chloride was supplied through the courtesy of the Smith, Kline & French Laboratories.

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cobaltous chloride therapy at a dose of 100 mg. per day. Seaman [5] also mentioned the case of a child who received 140 transfusions over a 10 year period who then showed active erythropoiesis after 164 days on oral cobaltous chloride at 25 mg. per day. Further details of this case are not given.

Rohn and Bond [6] described the case of an 81 year old man with anemia and marked hypocellularity of the bone marrow who showed a normal bone marrow 18 days after the institution of cobalt chloride therapy at a dose of 200 mg. per day. The validity of this case may be questioned, since refractoriness to other therapeutic agents was not demonstrated and no follow-up was available. They also described the case of a 23 month old infant with pancytopenia and extreme hypocellularity of the bone marrow who showed a response of all cellular elements within two weeks after beginning 120 mg. of cobalt chloride daily. This pancytopenia occurred after a significant toxic exposure, and the authors note that it is possible that institution of therapy was coincidental with a spontaneous remission.

This paper describes a case of refractory macrocytic anemia with cellular bone marrow that showed a specific response to the administration of cobaltous chloride.

Case Report

A 33 year old single unemployed woman was admitted to the Peter Bent Brigham Hospital for the first time on July 19, 1949. She complained of numbness and tingling in the hands and feet and a 30 pound loss in weight over the previous year. These symptoms had become worse four months before admission, and she had begun to notice moderate fatigability. Eighteen months before admission she had weighed 179 pounds.

Past History: She had always tended to be overweight. Her dietary habits were poor. There was a history of moderate to heavy alcohol ingestion for 10 years. She had never had jaundice or any previous serious illness. During World War II she worked in administrative and inspecting departments of the Chemical Warfare Service. There was no history of toxic exposure.

Physical Examination: Blood pressure 130/80 mm. of Hg. Weight, 144 pounds. The patient appeared to be in good health. There was no jaundice. Several spider angiomata were noticed on the upper chest and shoulders. The liver was down 5 cm. below the right costal margin. The spleen was not felt. Neurologic examination was negative.

Laboratory Data: Serologic test for syphilis, negative. Urine examination, normal. Stools by guaiac test, negative. (See table 1 for hematologic data.) Blood urea nitrogen, 15 mg.%; protein, 6.5 gm. per 100 c.c.; albumin, 4.4 gm. per 100 c.c.; bilirubin, 1.24 mg.% on admission; later, 0.54; prothrombin time, 41%; circulatory studies, normal; thymol turbidity, 0; Bromsulphalein retention, 23.5%. Electrocardiogram, normal. X-rays of the chest and gastrointestinal tract, normal. A cholecystogram showed a nonfunctioning gall-bladder.

The patient was discharged from the hospital on a high protein, high calorie diet, multiple vitamins and concentrated liver injections. Seven weeks later, on September 9, the liver was down three fingerbreadths. Prothrombin time was normal. Bromsulphalein showed 14.5% retention. On October 21 the liver was two fingerbreadths below the right costal margin. On December 22 it was noted that the patient felt well, that her weight had stabilized at 135 pounds and that she was eating well. She was working without fatigue. On January 19, 1950, she was doing well but had resumed drinking. Total protein was 5.9 gm. per 100 c.c.; thymol turbidity,

TABLE 1

Summary of Hematologic Data

Date	Hematocrit	Mean Cell Volume	Reticulocytes	White Blood Cell Count	Platelets
7–14–49	40			7,700	
8– 8–49	44	96	2.4	8,900	
9– 9–49	42	105			
2– 4–53	30	134		3,200	
5–18–53	9	145	3.2	2,600	
5–20–53	18				
5–23–53	24			1,950	
5–25–53	22		1.8		
5–27–53	23			2,200	
6– 3–53	24		4.0	2,100	
6– 8–53	21		3.3	2,350	27,000
6–16–53	22		3.6	2,050	
6–18–53	20		3.3	2,050	
6–20–53	26			2,100	
7–29–53	23			2,500	
8–19–53	23		2.9	3,200	
9–16–53	23			2,800	40,000
9–30–53	23		2.5	3,350	32,000
10–14–53	27		6.0	2,750	54,000
10–28–53	29		4.8		71,000
11–18–53	33		4.6		48,000
12– 3–53	41		4.1		57,000
12–16–53	41		5.1	4,300	74,000
1–13–54	45	101.8	2.4		87,000
2–17–54	44			5,500	85,000
3–17–54	44			5,550	50,000
4–14–54	44				50,000
7–28–54	43				111,000

9; prothrombin time, 80%. On February 16 she was doing well but her appetite had not been good.

The patient failed to keep her appointments and was not seen again until January 30, 1953. At this time she gave a history of having two to three drinks each night. She complained of weakness, fatigue and anorexia of six weeks' duration. Her dietary history was very poor. She had been getting liver and iron given by a local physician. She had been working in an electronics factory as a supervisor. Some of the employees under her had been cleaning parts with benzene, but although she had noticed the odor of benzene she had not been in direct contact with it. (Later study by the Department of Labor and Industries showed the benzene concentration in the room air to be too low to measure.)

Physical examination showed pallor. The weight was 152 pounds. Temperature, 99.4° F. There were some questionable spider angiomata around the shoulders. Blood pressure, 130/80 mm. of Hg. The liver was barely palpable. The spleen was not palpable. Bromsulphalein showed 25% retention; bilirubin, 1.18 mg.%; total protein, 6 gm. per 100 c.c.; albumin, 4.3 gm. per 100 c.c. Gastric analysis showed no free acid. Iliac marrow aspiration showed a marrow of normal cellularity with a distinct macrocytosis. Some of the red cell precursors showed minimal megaloblastic changes. The bone marrow differential is given in table 2.

The patient then failed to keep her follow-up appointment and was not seen again until she was admitted to the hospital on May 18, 1953. At that time she gave a history of drinking one pint of port wine each day. Her diet had remained poor. For two weeks she had noticed increasing fatigue and a feeling of weakness plus a

TABLE 2

Date	Myeloid Cells	Proerythroblasts and Basophilic Normoblasts	Polychromatic and Orthochromatic Normoblasts	Myeloid-Erythroid Ratio
2–7–53	699	123	178	2.3
6–9–53	509	222	269	1.0

feeling of lightheadedness. She noticed some precordial pain with exercise and was unable to walk upstairs.

Physical Examination: Blood pressure, 110/50 mm. of Hg. Pulse, 85. Temperature, 99° F. There was no jaundice. The skin was pale. The fundi showed bilateral multiple fresh hemorrhages. There was no lymphadenopathy. The heart was enlarged to 10 cm. from the midsternum. There was a harsh systolic murmur. Liver and spleen were not palpable. There was 1 to 2 plus ankle edema.

Laboratory examination showed a hematocrit of 9. Blood urea nitrogen, 9 mg.%; total protein, 5.8 gm. per 100 c.c.; albumin, 4.0 gm. per 100 c.c.; blood sugar, 97 mg.%; prothrombin time, 69%; bilirubin, 1.38 mg.% total, 0.68 direct, 0.70 indirect; Bromsulphalein retention, 19%; thymol turbidity, 13 (normal, 0–40). Stools ranged from benzidine-negative to 2 plus. Gastric analysis showed no free acid even after histamine. Venous pressure, 170 mm. of saline; vital capacity, 2,500 c.c.; circulation time, 8 seconds; clotting time, 12 minutes; bleeding time, 6 minutes. An electrocardiogram was normal. The heart was moderately enlarged by x-ray. Barium enema was negative. A gastrointestinal series was negative except for a questionable mild gastritis. Bone marrow aspiration showed a cellular marrow, with the same general appearance as in February, 1953 (table 2 and figure 2).

The patient's course in the hospital is shown in figure 1. She was transfused initially and then given 30 micrograms of vitamin B_{12} daily for 10 days, without response. She was then given folic acid, 15 mg. intramuscularly daily for 12 days, without response. Over a six day period she received daily intravenous injections of 200 c.c. of an irradiated yeast supernatant known to be a potent source of growth stimulating substances.[7] Throughout this period her hematocrit and reticulocytes did not change significantly.

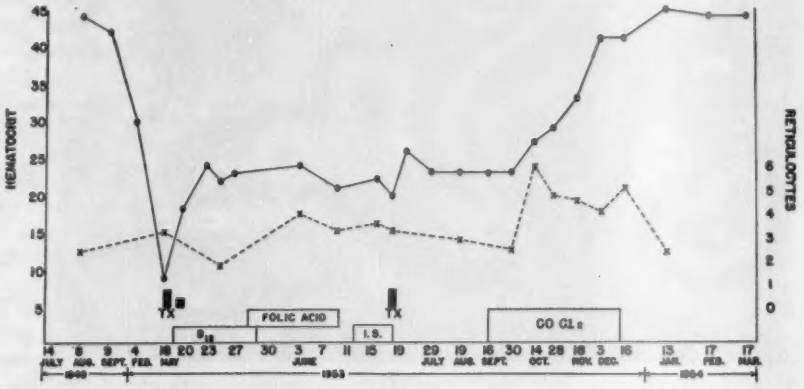

FIG. 1. The influence of treatment on the hematocrit and reticulocyte count. Note the changing time scale. o——o hematocrit. x- - -x reticulocytes. I. S., irradiated yeast supernatant.[7]

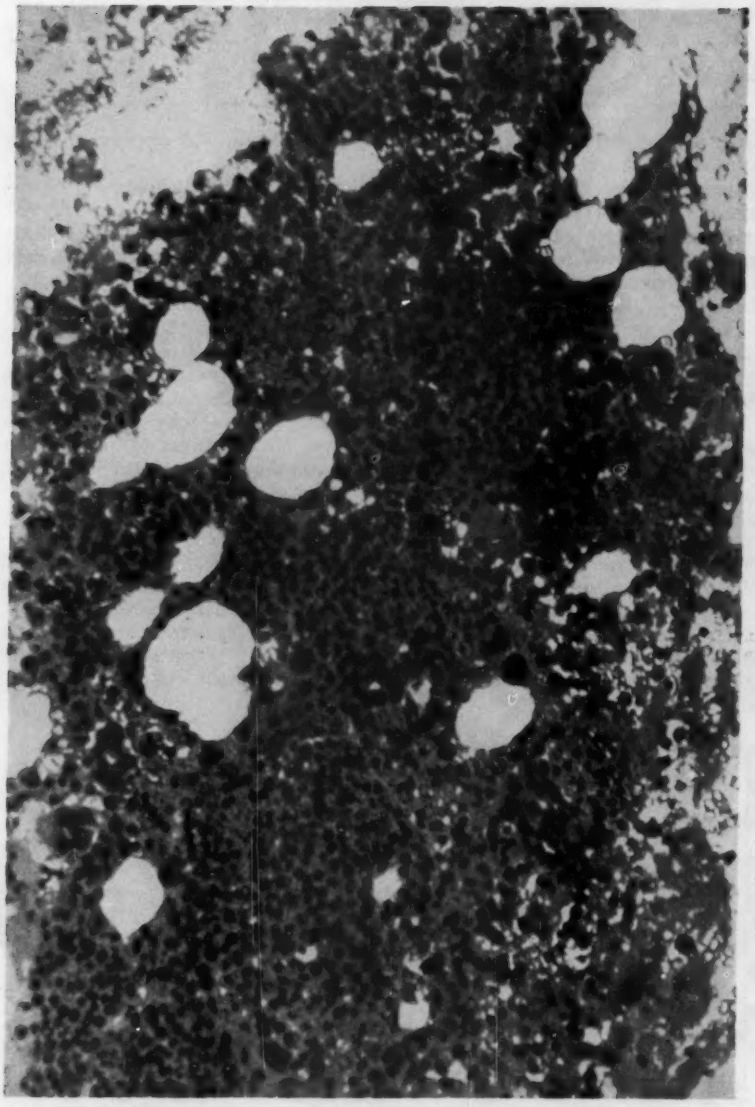

FIG. 2. A section of a bone marrow particle showing the cellularity of the marrow. (Stained with phloxin-methylene blue.)

The patient was discharged from the hospital on June 20, 1953, on a high protein, high calorie diet with supplemental vitamins. As may be seen from figure 1, she was then followed until September 16 without an appreciable change in her hematocrit. On that day she was started on cobaltous chloride.* She took 180 mg. a day until December 16 without noticeable ill effects. The reticulocyte count was 2.5% at the beginning of cobalt therapy. On October 14 it was 6.0%. The hematocrit went rapidly upward to a value of 41 on December 16.

Cobalt was discontinued on December 16. The patient continued to feel well. She followed her diet faithfully and drank no alcohol. She was assigned to another job which did not involve exposure to benzene. Since that time her hematocrit has been stable.

The patient was re-admitted to the hospital on June 22, 1954, for an episode of acute pancreatitis which followed approximately one month of moderate alcohol ingestion. At that time her hematocrit fluctuated due to changes in fluid balance, but it was 43 without transfusion at the time of her discharge on July 17.

Discussion

Refractory anemia has been characterized as an anemia that does not respond to any known treatment with the exception of blood transfusion.[8] This broad group of refractory anemias can be subdivided into a number of different types, depending on the cellularity of the bone marrow, the size of the red cells, and the presence or absence of associated leukopenia or thrombocytopenia. Such classification has generally been of academic interest only, but it may become quite important in the management of these cases as additional therapeutic agents are found to be of value. The four cases of refractory anemia that have been reported to respond to cobalt administration [4, 5, 6] have all been associated with red cells of normal size and aplasia of red cell precursors in the marrow. The present case is the first report of a macrocytic refractory anemia with cellular bone marrow to respond to cobalt.

Bomford and Rhoads [8] noted that damage to the liver in varying degrees is an important factor in the etiology of refractory anemia. In their series of 26 patients tested, 14 showed at least one abnormal liver function test. Our patient was known to have had a mild degree of liver disease four years before the onset of her anemia, and impaired liver function is still present after recovery from the anemia. In this case liver disease may be an important conditioning factor, but it is apparently not the only factor involved.

In the Bomford and Rhoads series of 66 patients, 24 were known to have been exposed to potentially toxic substances, 11 of which represented exposure to benzene. For 11 months before the development of anemia our patient had worked in a room where small amounts of benzene had been in use. Although the benzene exposure was minimal, it is well known that bone marrow depression by toxic agents is not a function of dose.[9] The antecedent liver disease may well have made this patient more susceptible to benzene. Macrocytic anemia and a cellular marrow are known to occur after exposure to benzene.[10] Kleinberg et al.[11] reported that cobalt counteracted the inhibitory effect on erythropoiesis of benzene administration in rabbits. Their data, plus the recovery of this patient, suggest that cobaltous chloride should be used for anemia following benzene exposure, perhaps as soon as possible after exposure.

* Generously supplied by Smith, Kline and French Laboratories.

In a series of 58 cases Bomford and Rhoads [8] noted 15 spontaneous remissions and eight cases of temporary improvement. They noted that remissions were more common in patients whose disease could be attributed to exposure to an exogenous toxin. In view of this natural recovery rate, it is possible that this patient may have had a spontaneous remission. However, after receiving vitamin B_{12} and folic acid, she was then given a good diet and multiple vitamins and followed for a period of four months. During this time the hematocrit was stable at a level of 23. The immediate response in reticulocytes and hematocrit to cobalt makes it very unlikely that a spontaneous remission was involved. One may speculate that the slow recovery of the leukocytes and platelets represented the natural rate of recovery, and that the rapid erythropoietic recovery was due to cobalt.

A large number of therapeutic agents has been tried in the treatment of the refractory anemias. Roelsen and Ohlsen [12] have recently described an interesting case of refractory megaloblastic anemia and have reviewed the literature. In this type of anemia, after eliminating the possibility of response to vitamin B_{12} or to folic acid, no definite response to any growth-stimulating substance or vitamin preparation has been noted. Loeb, Moore and Dubach [13] described 10 cases of refractory anemia and discussed the value of ACTH, cortisone and splenectomy in this condition. They noted striking clinical improvement after splenectomy in four instances, and from continuous cortisone administration in one instance. None of their cases demonstrated a macrocytosis, and it is therefore probable that they did not represent the same type of anemia present in our case.

Summary

A case is reported of macrocytic refractory anemia with cellular bone marrow that responded to cobaltous chloride therapy. The value of cobaltous chloride in refractory anemia is discussed.

Summario in Interlingua

Le majoritate del investigatores ha trovate que cobalt ha nulle valor in le tractamento de anemia refractori. Nonobstante, un revista del litteratura revela quatro casos de anemia refractori con medulla ossee hypocellular que respondeva favorabilemente al administration de cobalt.

Es describite le caso de un femina de 33 annos de etate suffrente de un macrocytic anemia refractori. Le patiente habeva un historia de alcoholismo in forma moderate con cirrhosis precoce e etiam un historia de exposition minime a benzina. Illa arrivava al hospital con un hematocrite de 9 e un volumine cellular median de 145. Le medulla ossee esseva cellular. Illa esseva tractate con vitamina B_{12}, acido folic, e irradiate extracto de levatura. Iste therapia resultava in nulle melioration. Post un periodo de controlo de quatro menses le patiente recipeva chlorido de cobalt in un dosage de 180 mg per die. Il sequeva un immediate responsa del reticulocytos, e le hematocrite retornava a valores normal.

Le recuperation de iste patiente indica que cobalt merita essayos additional in le therapia de anemia refractori, specialmente in casos con un historia de exposition a benzina.

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MACROGLOBULINEMIA OF WALDENSTRÖM: A REVIEW OF THE LITERATURE AND PRESENTATION OF A CASE *

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MACROGLOBULINEMIA was first described as an entity by Waldenström in 1948,[1] in discussing six patients seen by him in Upsala, Sweden. By means of ultracentrifugation of the patients' sera he was able to demonstrate the presence of a fraction in the serum proteins—presumably globulins—with molecular weights near 1,000,000, in contrast to the highest normal globulin molecular weights of 150,000.

Other cases have been reported sporadically from Europe. In 1950 Tischendorf and Hartmann [2] reported one case, Bichel, Bing and Harboe [3] another. Schaub added three cases in 1952 [4] and one in 1953.[6] Habich [5] in 1953 studied the sero-immunologic properties of macroglobulins and reported these findings on 11 previously unreported patients, along with five cases published elsewhere in the literature. Wilde and Hitzelberger [9] reported three cases, Mandema [10]

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two cases, and Muller [8] one case in 1954. Other authors have reported clinically similar cases,[10–14] in whom the final diagnostic proof of macroglobulinemia was not obtained and who are therefore excluded from this report. The case herein appears to be the first reported from outside Europe.

The disease or syndrome as originally described by Waldenström was separated from other, somewhat similar entities by the demonstration with ultracentrifugation of giant protein molecules. Waldenström's patients, and the patients of other authors, have shown certain clinical and laboratory findings with sufficient regularity to warrant their inclusions as significant characteristics of the syndrome.

1. It is predominantly an affection of males over the age of 50.
2. There are weakness, weight loss and pallor.
3. Nasal and oral hemorrhages occur frequently.
4. Subarachnoid and ocular hemorrhages are common.
5. Lymphadenopathy and hepatomegaly are often present.
6. Laboratory findings are those of hyperglobulinemia, anemia, extremely elevated erythrocyte sedimentation rate, demonstrable euglobulins and positive formol-gel reaction, and frequently there is spontaneous gelification of the serum on cooling to room temperature or lower. Serum viscosity is exceptionally high. White blood count and platelet counts are usually normal, and bleeding and coagulation times are not usually prolonged.

The bone marrow shows a fairly uniform (but often confusing) morphology, consisting of an increase in mononuclear cells that are variously described as "lymphoid," "benign plasma cell overgrowth" and "unripe plasma cells." [7, 9, 11] Tischendorf describes the bone marrow picture as consistent with that of a lymphoid reticulosis.[2] None of the bone marrows shows a pattern diagnostic of multiple myeloma; further, none of the typical bony defects is evident radiographically.

The following case is presented because it meets a majority of the characteristics previously described and because the diagnosis was substantiated by ultracentrifugation of the patient's serum.

Case Report

A 50 year old white cement worker entered Minneapolis General Hospital on February 7, 1955, because of nosebleeds, weakness, weight loss and persistent bleeding from the site of a recently extracted tooth. The patient stated that he had been admitted three times to a private hospital during the previous two years for undiagnosed gastrointestinal bleeding and ocular hemorrhages. Whole blood transfusions were administered on each occasion.

Physical examination disclosed a pale, weak, chronically ill middle aged male with normal vital signs. There was a crusted, vesicular herpetic eruption of the left forehead, with involvement of the conjunctivae but not of the cornea. Funduscopic examination showed numerous retinal hemorrhages bilaterally, with engorgement of the veins. There was evidence of recent hemorrhage in both nares, but no site of origin could be ascertained. The site of the extracted tooth was oozing blood. The lymph nodes were not enlarged except for a few shotty, nontender inguinal nodes.

Examination of the lungs disclosed no abnormality. On cardiac auscultation there was a grade II (Levine) apical systolic murmur without transmission. The liver was 6 cm. below the right costal margin and moderately tender, with a smooth, rounded edge. The spleen was not palpable. The remainder of the physical examination was unremarkable.

Laboratory data showed a negative serologic test for syphilis. The hemoglobin was 7.0 gm.%, with a hematocrit of 21%; red blood cells, 2.17 million per cubic millimeter; the white blood cells, 7,700 per cubic millimeter, with 67% granulocytes, 29% lymphocytes, 2% monocytes and 2% eosinophils. Reticulocytes were less than

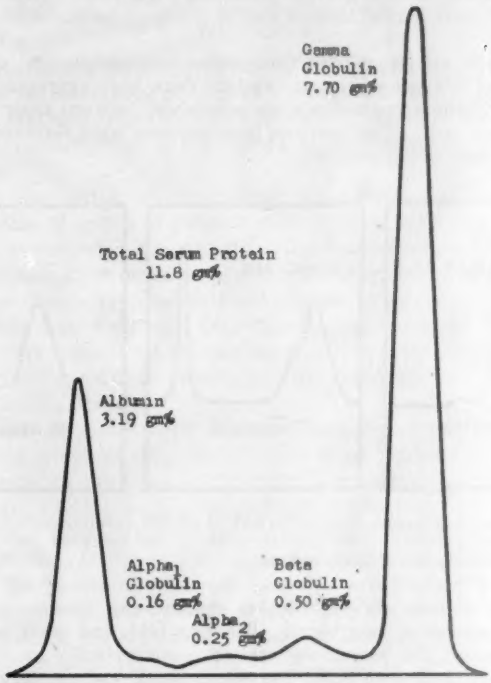

FIG. 1. Densimetric graphing of the electrophoretic pattern of the patient's serum shows that the majority of the globulin is in the gamma zone, and, further, that these molecules are homogeneous in their migration pattern.

0.3%. The platelet count was 240,000 per cubic millimeter. The erythrocyte sedimentation rate was 11 mm./hour, and, later, 29 mm./hour * (Westergren). The bleeding time was 8½ minutes; the Lee-White coagulation time, 38½ minutes. The formol-gel test was positive and the test for cryoglobulins negative. The one-stage prothrombin time was 18.1 seconds (control, 12.7 seconds). Several urinalyses were normal, with no Bence Jones protein demonstrated.

Blood chemistry studies showed a blood urea nitrogen of 20 mg.%; total protein, 12.0 gm.% (albumin, 3.2 gm.%; globulin, 8.6 gm.%; fibrinogen, 0.191 gm.%). The liver function tests showed a total serum bilirubin of 0.3 mg.%, 5% Bromsulphalein

* See second admission.

retention after 45 minutes, a negative cephalin-cholesterol reaction, a thymol turbidity of 4.5 Maclagan units, and an alkaline phosphatase of 2.8 King-Armstrong units.

Coagulation studies showed a decreased prothrombin content in the plasma, with decreased prothrombin consumption (conversion of prothrombin to thrombin), indicating a defect of both the first and second stages of coagulation. Intravenous vitamin K_1 produced no decrease in the one-stage prothrombin time. Tests for circulating anticoagulants were negative. Fibrinolysin was absent. Factor V and Factor VII of Owren were normal.

The whole blood specific gravity was 1.054; the plasma specific gravity was 1.042. Electrophoresis showed that, of the 8.6 gm.% globulin, 7.7 gm.% was gamma globulin.

A bone marrow aspiration from the sternum failed to disclose any cells or patterns diagnostic of multiple myeloma. Rather, there were aggregates of cells, perivascularly located, whose resemblance lay somewhere between those of lymphocytes and those of plasma cells. Two previous bone marrows were reviewed which showed even greater numbers of "plasma cells."

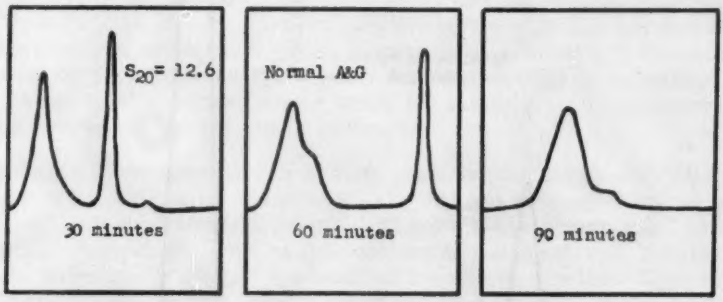

FIG. 2. Ultracentrifugation was performed at 60,000 revolutions per minute (240,000 times the force of gravity). Salt concentration of the specimen was 0.5 molar. The homogeneity of the molecules is again evident.

A radiographic bone survey failed to disclose any abnormality of the skull, vertebrae, ribs, sternum or long bones. The lung fields and heart were normal.

Hospital Course: The patient was treated symptomatically for the herpes zoster ophthalmicus, transfused with 2,500 c.c. whole blood, and discharged to his home after two weeks' hospitalization without a definite diagnosis.

The patient was re-admitted six days later, comatose and nearly exsanguinated. Bleeding from the lower gastrointestinal tract was profuse. The neck was rigid. Neurologically there were right-sided hyperreflexia and a right-sided Babinski reflex. Laboratory data: hemoglobin, 3.9 gm.%; red blood cells, 1.70 million per cubic millimeter; hematocrit, 12 vol.%; white blood cells, 13,400 per cubic millimeter, with 83% granulocytes, 15% lymphocytes, 1% monocytes and 1% eosinophils. The platelet count was 200,000 per cubic millimeter; the bleeding and capillary coagulation times were normal, with a one-stage prothrombin time of 14.9 seconds (control, 13.0 seconds). The erythrocyte sedimentation rate was 156 mm. in 30 minutes and 165 mm. at one hour (Westergren). A spinal tap showed 10,600 erythrocytes (25% crenated). Several urinalyses were again normal, with no demonstrable Bence Jones proteinuria. Serum proteins had fallen to a total of 7.2 gm.% (albumin, 2.7 gm.%; globulin, 4.5 gm.%).

Ultracentrifugation performed at the University of Minnesota School of Veterinary Medicine demonstrated the presence of macroglobulins having a sedimentation constant of 12.6 Svedberg units, equivalent to a molecular weight of approximately 400,000 (normal, 150,000). These macromolecules were very homogeneous, producing a very narrow, high peak.

Course: Because of the patient's severe agitation, intramuscular chlorpromazine was used with good results. The patient received 9,000 c.c. whole blood, with a consequent rise in hemoglobin to 13.0 gm.%, with a hematocrit of 39%. Repeat one-stage prothrombin times averaged two seconds above the control. Clinical response to blood replacement was satisfactory and the patient was discharged to his home.

Discussion

Clinical classification of this syndrome is difficult; its relationship to purpura hyperglobulinemica [1] is poorly understood. It may, indeed, be a variant thereof. Other authors feel that it is (a) a rare variant of multiple myeloma,[10] (b) the Bing-Neel syndrome,[13, 14] or (c) a variety of plasmacytoma or an altered immunization reaction.[7]

Pederson [1] was unable to demonstrate the presence of macromolecules in ultracentrifugation of serum of patients with multiple myeloma. Both Waldenström [1] and other authors [2, 3, 9] insist upon the demonstration by ultracentrifugation of macromolecules in order to establish the diagnosis of macroglobulinemia. Habich [5] rather thoroughly studied the antigenic properties of these "paraproteins" and demonstrated through the immune sera of rabbits that 14 of the 16 cases studied were capable of developing disease-specific antibodies. He suggests that immunologic studies can suggest the diagnosis, but that ultracentrifugation yields the final proof.

From the case presented here it is suggested that there is a multiplicity of defects of protein synthesis, only one of which is the production of giant globulin molecules; a study of the cases of the other investigators tends to corroborate this. Indeed, by electrophoresis the globulin macromolecules can be found in the gamma zone,[5] beta zone [1, 2, 3] and zeta zone.[3] Mandema [10] reported decreased prothrombin content to the plasma and decreased AC-globulin (Owren Factor V). The presented case manifested decreased prothrombin and decreased fibrinogen. All cases except two [3, 10] and the present one have shown pathologic amounts of euglobulin. The cases of Tischendorf,[2] Habich,[5] Schaub [6] and Mandema [10] showed less than 3 gm. % albumin. Several cases have had Bence Jones proteinuria.

Treatment has been colorful and varied, prompted undoubtedly by a lack of knowledge of the real genesis of the disease and aggravated by the poor prognosis. Ciba Amidin 2834-37 produced a decrease in marrow lymphocytosis and reversion of the euglobulin test to negative in a case of Wilde and Hitzelberger,[9] but there was a reversion of the euglobulin test to positive shortly after treatment was discontinued. Nitrogen mustards, P_{32} and Amidin were without effect on their second case. Cortisone and vitamin K have been without significant effect. At present, whole blood replacement appears to offer the only hope.

Summary

A brief review of some of the cases of Waldenström's macroglobulinemia is made, together with the usual historical, physical and laboratory findings.

A case of macroglobulinemia is presented which manifests a marked hemorrhagic diathesis.

It is suggested that this syndrome represents a pathologic process wherein protein synthesis is defective in many facets and not just limited to the formation of macroglobulins.

Treatment to date has been supportive with whole blood replacement, little if any therapeutic success having been obtained by chemotherapeutic agents.

ACKNOWLEDGMENT

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SUMMARIO IN INTERLINGUA

In 1948, Waldenström de Sveda studiava plure patientes con hyperglobulinemia e associate tendentias sanguinatori. Per medio de studios ultracentrifuge del seros de un numero del patientes, ille succedeva a demonstrar gigante moleculas de globulina con un peso molecular in le vicinitate de 1.000.000. A iste gruppo Waldenström attribueva le nomine de "macroglobulinemia." Ab 1948 usque al fin de 1954 plure demonstrate casos additional ha essite reportate in le litteratura europee.

Secundo le description original de Waldenström, iste syndrome es predominantemente un affection de masculos supra le etate de 50 annos. Illo es essociate con debilitate, perdita de peso, pallor, e hemorrhagias ab le membranas mucose, e le constatationes laboratorial de hyperglobulinemia, anemia, e extreme acceleration del sedimentation erythrocytic. Studios additional de laboratorio demonstrava euglobulinas, un positive reaction formol-gel, e altissime viscositate seral.

Es presentate le caso de un masculo blanc de 50 annos in qui le constatationes historic, physic, e laboratorial esseva typic. Le therapia esseva primarimente supportative. Sanguine integre esseva administrate in quantitates massive a causa del presentia de hemorrhagias gastro-intestinal.

Es discutite certe ideas relative al natura de iste morbo.

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EDITORIAL

THE EFFECT OF CORTISONE AND RELATED STEROIDS ON THE CARDITIS OF RHEUMATIC FEVER

THE highly favorable immediate effects of ACTH and cortisone in rheumatic fever were described by Hench et al.[1] soon after their first report of their effectiveness in rheumatoid arthritis. The fever, malaise, tachycardia and other systemic symptoms of the acute illness as well as the pain and local inflammation of the arthritis subside with remarkable rapidity and great regularity, although all too prone to recur promptly if treatment is stopped prematurely. These effects, however, are not radically different from those which may usually be obtained from salicylates in adequate quantities. Although the relief from cortisone in full doses is perhaps obtained a little more certainly and promptly, it is doubtful whether in the average patient this alone outweighs the adverse reactions and the risk involved. The mortality from acute rheumatic fever, even in the early phase, as well as the late disability stems largely from the cardiac involvement. To furnish a significant advantage, cortisone must be capable not only of shortening the duration of the illness and reducing its inherent severity but of preventing or arresting the carditis. Regarding this there is still sharp difference of opinion.

Since rheumatic fever is a self-limited disease, extremely variable in its severity and the duration of its manifestations, it is difficult to assess the value of any therapeutic procedure. It has proved almost impossible to secure an adequate series of controls. One of the best studies of this type is that of Graef et al.[2] who compared 50 cases treated with salicylate or vaccines with 105 controls who received no salicylate or other antipyretic or "specific" drug. Of these latter, 47 were followed throughout the acute course and for two weeks of subsequent observation. The duration ranged from 24 days to over five months and the single cycles of fever from five to 56 days. The temperature tended to fall spontaneously. In 22 of 29 cases the arthritis subsided within a week, and it recurred in less than half of these. There is no precise information regarding the incidence of cardiac lesions except that 12 of the 47 had chronic carditis at the onset of the study. Graef's observations offer abundant evidence that the acute manifestations subside spontaneously, but they do not constitute dependable data for comparison with series of patients treated differently in other clinics and at other times.

[1] Hench, P. S., et al.: Effects of adrenal cortical hormone 17-hydroxy-11-dehydrocorticosterone (compound E) on acute phase of rheumatic fever: preliminary report, Proc. Staff Meet., Mayo Clin. **24**: 277–297, 1949.

[2] Graef, I., et al.: Studies in rheumatic fever. I. The natural course of acute manifestations of rheumatic fever uninfluenced by "specific" therapy, Am. J. M. Sc. **185**: 197–210, 1933.

A number of reports of studies by individual groups have been published, most of which have been inadequate in the number of subjects and particularly in lack of controls. These have been contradictory, as might have been expected, ranging from the favorable reports of Kelley [3] and Greenman et al.[4] to those of Johnson and Ferencz [5] and of Rowe et al.[6] who observed no better results than had been obtained without hormone therapy. A more adequate report has been made by Massell,[7] who supplemented the observations of his own group by an exhaustive review of the literature (in English) over about a five year period, compiling as many data as possible regarding the effect of cortisone on each of the major manifestations of the disease.

As to the effect on fever and arthritis, there is no question. Much stress has been laid on the behavior of the subcutaneous nodules, because of their histological similarity to the lesions in the valves. Pertinent data, available in only 30 cases, indicate that with adequate doses new nodules did not appear during treatment and in most cases they became smaller or disappeared. No dependable conclusions could be reached regarding its effect on the cutaneous eruption or on chorea.

The sedimentation rate is almost invariably reduced to normal, as it is also by salicylates, but there is controversy as to whether this results from arrest of the active pathologic process or merely from a direct action in reducing the formation of plasma fibrinogen and globulin. This does not indicate eradication of the disease or offer any assurance against a severe relapse if cortisone is withdrawn.

More significant would be evidence of its influence on carditis. Pericarditis was observed in 64 cases, and it disappeared under observation in 54. Its duration as determined by persistence of the friction rub, a rather treacherous criterion, was less than a week in 24 of 44 cases, and in 16 of 19 of these (with necessary data) less than four days. The duration of pericarditis in cases otherwise treated is notoriously variable. Shortening of a prolonged P-R interval was recorded in 82 per cent of 66 patients under treatment, but this also varies greatly and unpredictably and is of questionable significance.

More suggestive was the relief of congestive failure in 30 of 40 patients under treatment (a low salt diet was usually required). Since there is no response to cortisone in cases in which the failure results from mechanical insufficiency of the valves or from extensive long standing disease of the

[3] Kelley, V. C.: Corticotropin (ACTH) therapy of initial attacks of acute rheumatic fever in children, Am. J. Dis. Child. **84**: 151–164, 1952.

[4] Greenman, L., et al.: Cortisone therapy of initial attacks of rheumatic carditis, Am. J. Dis. Child. **89**: 442–450, 1955.

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[7] Massell, B. F.: ACTH and cortisone therapy of rheumatic fever and rheumatic carditis, New England J. Med. **251**: 183–190, 221–227, and 263–270, 1954.

myocardium, these results were regarded by Massell as "strongly" suggestive "that the manifestations of carditis are frequently influenced favorably" and "that the rheumatic inflammatory process responsible for these manifestations can be suppressed by the hormones."

Somewhat more suggestive are the data regarding "significant" heart murmurs as indicating prevention or arrest of valvular disease. All diastolic murmurs and apical systolic murmurs were regarded as significant but not isolated basal systolic murmurs. Data were collected in 193 cases. Of 73 observed during a recurrence, murmurs disappeared in only 3 per cent. Of 120 seen during the initial attack, murmurs disappeared in 39 cases. The frequency of disappearance varied inversely with the duration of illness before treatment was started. Thus it varied from 94 per cent of 16 cases in which treatment was started during the first week to 6 per cent of 35 cases started after the sixth week. He also tabulated the number of cases showing such murmurs after completion of treatment, classified according to the duration of illness before treatment was started. The frequency rose abruptly from 6.5 per cent of 31 cases starting treatment during the first week and 49 per cent of 35 cases starting during the second week to 90 per cent of those not treated until after the sixth week. Most observers who have reported favorably have stressed the importance of early treatment.

Massell's data regarding cardiac enlargement and its subsidence under treatment show a similar relationship to the duration of the illness before treatment was started. Interpretation is complicated, however, by the disturbing effect of pericarditis.

Massell's data offer no convincing evidence that the duration of the disease is shortened if rebounds and immediate relapses are considered. Although having an impression that the duration was shortened in some treated cases, he concludes that "*so far* the weight of evidence favors the view expressed by Barnes and Hench that cortisone and ACTH are highly suppressive of rheumatic inflammation but that they do not actually halt or shorten the duration of the pathologic process."

The data presented by Massell regarding murmurs are perhaps less significant than they appear. It seems unlikely that all the systolic apical murmurs that disappeared were indicative of carditis or valvular disease. He was unable to distinguish "significant" from presumably insignificant murmurs on the basis of published descriptions. It is also likely that the group in which treatment was begun late in the disease was weighted with a higher proportion of severe cases than the early group. The results, nevertheless, are impressive, and they show the importance of an early start, perhaps a matter of days rather than weeks, of effective doses, and of treatment of adequate duration, irrespective of mere symptomatic relief.

Among the more favorable reports, that of Greenman et al.[4] should be noted. They treated 53 children with clinically definite acute carditis during their initial attack (and two of these again during a second attack).

Large doses (300 mg. cortisone daily) were given for six weeks with gradual reduction during the subsequent two weeks. All had significant murmurs. A faint apical systolic murmur without other sign of cardiac disease was disregarded. Cardiac enlargement was found in 30 and congestive failure in 24 of these. After treatment 25 showed no cardiac abnormality and four more only a faint apical systolic murmur. Twelve had (significant) murmurs only, and 12 others enlargement with valvular lesions.

Four cases had an acute recurrence when treatment was stopped, controlled by a second course of treatment but with residual cardiac damage. Several others had transient trivial rebounds, characterized by some fever and acceleration of the sedimentation rate. In this series, too, there was a striking correlation between early treatment and recovery from the carditis. Of 14 patients starting treatment within two weeks, 12 recovered, and 16 of 27 starting during the third to the sixth week. Only one of 14 not treated within six weeks became normal. The two patients treated during a subsequent attack (not an immediate resurgence) again escaped evident cardiac damage.

Greenman did not find evidence that the duration of the attack was shortened. Adverse reactions were often troublesome but serious only in one patient, a psychosis in a girl of 15. It is striking how rarely these children show the commoner serious reactions of adults, such as psychosis, peptic ulcer, and osteoporosis with fractures.

Greenman's work meets many of the doubts and criticisms that may be leveled at Massell's collected statistics, but the number of cases is still small. Further a seemingly normal cardiac status when cortisone is withdrawn is no guaranty that even without a frank relapse slowly progressive scarring or even persisting low grade active carditis may not lead to valvular lesions later. This can be determined only by years of observation.

The most comprehensive investigation of this subject now available is the Comparative Clinical Trial of ACTH, Cortisone and Aspirin, carried out under the auspices of the Medical Research Council of Great Britain and the American Heart Association. A detailed report of the earlier phases of this study has recently appeared.[8] This study included 500 children under 16 years of age in 12 clinics, equally divided between the two nations. Equal numbers were assigned to each of three groups for treatment with ACTH, with cortisone, and with aspirin. Deliberate selection of cases was carried out to ensure uniformity as to the season of the year and the duration of the illness before treatment, forming three subgroups under each major group: those beginning treatment during the first two weeks, during the third to sixth week, and later than six weeks. For uniformity in other respects the observers depended upon random selection of cases,

[8] The treatment of acute rheumatic fever in children. A coöperative clinical trial of ACTH, cortisone and aspirin, Circulation 11: 343–377, 1955.

and subsequent analyses showed no significant difference between the groups. Great care was taken to insure such random selection and to secure uniformity in dosage, general management, methods of study and data recorded. Patients were treated for six weeks, those on cortisone receiving 100 mg. per day for four weeks (after a few days of larger priming doses), then gradual withdrawal. Patients were observed closely for three subsequent weeks, then at intervals for one year. In the entire group there were six deaths and 39 cases were retreated.

In analyzing the results obtained, cases were classified according to the condition of the heart before treatment rather than the duration of the illness: A, no carditis; B, acute carditis but no previous damage; C, old cardiac disease from previous attacks with presumable flareup. In over half the cases treatment was started within two weeks of the onset (in about 30 per cent within one week), and about two-thirds gave no history and showed no evidence of a previous attack. Adverse reactions were encountered but are not reported in detail. In general as far as arthritis, fever, and systemic manifestations are concerned, the usual favorable results were obtained. Subcutaneous nodules often disappeared. Patients without murmurs at the onset rarely developed them during treatment, and only one in eight showed murmurs at the end of the year. Soft apical systolic murmurs disappeared in many cases, more frequently in those receiving hormones, but no difference was made out between the three groups after the year's observation. After exhaustive analyses, the conclusion was reached that there was "no evidence that any of the three agents resulted in uniform termination of the disease." The hormones effected more prompt control of some acute manifestations, but there was more "rebound" when treatment was stopped, and no significant difference could be detected after a year.

In spite of the need for impartial and dispassionate consideration, one must feel disappointment at the paucity of the therapeutic results obtained or at least at the failure of the hormones to show any advantage over aspirin. The group receiving salicylate probably comes as near to being a control group as it is feasible to obtain. The study was obviously planned with care and carried out with precision. In retrospect, however, it is subject to criticism in two respects. The size of the dose of hormones was too small and the duration of treatment too short to ensure optimum results. It seems probable that at least eight and possibly 12 weeks might be needed in many cases. Premature or repeated interruptions to test for activity, with disturbing rebounds,[9] may well augment the carditis as well as be uncomfortable. Furthermore the total dose administered during the six weeks was less than a third of that used by Greenman [4] over an eight weeks period.

The situation in acute rheumatic fever is different from that in rheumatoid arthritis in which treatment may be lifelong, excessive doses are

[9] Fischel, E. E., et al: Observations on treatment of rheumatic fever with salicylate, ACTH and cortisone, Medicine 31: 331–355, 1952.

pointless, and the dose must be restricted to the minimum that makes life tolerable. In a self limited disease like rheumatic fever it should be feasible in most cases to administer larger doses of cortisone for periods which are limited but yet may run for several months, especially in children who rarely show serious adverse reactions.

The observations currently available are, indeed, not highly encouraging as to the possibility of controlling rheumatic carditis with cortisone. Continued trial on a large scale, however, is strongly indicated, starting early in the attack, with adequate doses and concentrating on subjects without chronic cardiac disease. If such a trial fails to show its effectiveness in this respect, there seems to be little reason for using cortisone routinely in the treatment of rheumatic fever.

PAUL W. CLOUGH

REVIEWS

Clinical Disorders of Hydration and Acid-Base Equilibrium. By LOUIS G. WELT, Professor of Medicine, Department of Medicine, University of North Carolina. 262 pages; 14.5 × 22 cm. Little, Brown & Co., Boston. 1955. Price, $6.00.

This book is an excellent exposition of the "Yale School" of fluid and electrolyte philosophy. As such it presents a fairly static view of the inorganic metabolism, and relies for therapeutic guidance to a great extent upon calculations of deficits based upon analyses of accessible body fluids which the author admits are grossly inadequate.

Outstanding in this book is the chapter on renal physiology, a field to which the author has made many valuable contributions. This, the longest chapter in the book, makes the volume a worthwhile addition to a clinical library.

The clinical discussions of various problems are good. The choice of cases as illustrations of particular points has not been uniformly illuminating, since details of therapy are not always presented until a particular point is reached. In that way little background is available for study of the problem being discussed.

From a clinical standpoint the two last chapters, on the management of edema and on acute renal insufficiency ("Acute Tubular Necrosis" or lower nephron nephrosis), are invaluable. Here again the author reveals his insight into renal problems and imparts an excellent background for the understanding and suggestions for the management of those two vexing clinical problems. The suggestions for the prevention of acute tubular necrosis, alone, are worth the price of the book.

The organization and presentation of material are good and the book is remarkably free of minor errors, indicating a painstaking job of editing and proofreading.

SAMUEL P. BESSMAN

Cardiology Notebook for Preliminary Instruction in Medical Curricula. Editorial Board: ALFRED P. FISHMAN, M.D., Chairman, and others. 97 pages; 20 × 26 cm. Grune and Stratton, Inc., New York. 1955. Price, $2.50.

This notebook is designed for the medical student and aims to make available a few examples of the method and language of cardiology in the simplest form. Subject matter is divided into the following four sections: (1) cardiac fluoroscopy and x-ray, (2) electrocardiography, (3) hemodynamics, (4) nomenclature and cardiac diagnosis.

There are numerous full page illustrations of fluoroscopic views, x-rays and electrocardiograms with the readings and interpretations, as well as a section on the opposite page for notes by the students.

The text does not strive to be complete. Its value might have been enhanced by more complete orientation and emphasis on basic concepts, rather than specific records. It will not serve as a reference text, but may be useful for the beginning medical student.

L. S.

The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology, and Therapeutics for Physicians and Medical Students. 2nd Ed. By LOUIS S. GOODMAN, M.A., M.D., Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, Utah; and ALFRED GILMAN, Ph.D., Professor of Pharmacology, College of Physicians and Surgeons, Columbia University, New York, N. Y. 1,831 pages; 18 × 26 cm. The Macmillan Company, New York. 1955. Price, $17.50.

The objectives of the popular first edition have been retained in the second edition of this book, namely, the correlation of pharmacology with the medical

sciences, the interpretation of the actions of drugs from the viewpoint of important advances in medicine and the placing of emphasis on the applications of pharmacodynamics to therapeutics. The authors state that they have made a special effort to provide the reader with a "way of thinking about drugs" so that he will be able to evaluate critically the published literature on the many new therapeutic agents. The organization of the subject matter remains essentially the same as the first edition. The present edition reflects the extensive advances in pharmacology and therapeutics which have marked the 14 years since the book first appeared.

Well documented descriptive material is interspaced throughout the discussions of drug actions. This reference work shows excellent integration and the physician is provided with a critical survey of each topic. The bibliography includes numerous specific references as well as monographs and reviews, all in alphabetical arrangement at the end of each chapter for easy use.

As in all modern textbooks of pharmacology, the impact of organic chemistry (structure vs. activity relationships) and biochemistry (enzymatic action of drugs) makes its imprint. The authors have achieved a magnificent task in presenting difficult material in a clear, readable style.

As an encyclopedia of modern pharmacology, the volume will continue to be a standard reference source for the practicing physician.

C. JELLEFF CARR

International Pharmacopoeia. 1st Ed., Volume II. 350 pages; 16 × 24.5 cm. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. 1955. Price, $6.75.

The publication of Volume II of the International Pharmacopoeia successfully completes a task begun in 1937 under the auspices of the League of Nations Health Organization and carried on since 1947 by the World Health Organization, through the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, and other specialists.

This volume consists of 217 monographs, 26 appendices, and 1 annex. It contains, among others, specifications for some of the pharmaceutical preparations introduced into therapeutics during the last few years (e.g., penicillin, chloramphenicol, dihydrostreptomycin, oxytetracycline) and for some synthetic substances of growing importance. It also contains monographs on compressed and sterile injections included in Volume I.

This Pharmacopoeia shows great care in preparation. One is impressed by the fact that many of the old-fashioned tinctures are official in this new volume, such as tincture of nux vomica and tincture of aconite.

The description of the tests to establish the identity and purity of remedies recognized in this volume are of the highest degree of scientific precision. A special feature of the International Pharmacopoeia is a table of usual and maximal doses for adults and another for children of different ages.

It is hoped that this volume published under the World Health Organization will tend to simplify and unify the prescribing of drugs on an international basis.

JOHN C. KRANTZ, JR.

Medical Greek and Latin at a Glance. 3rd Ed. By WALTER R. AGARD, B. Litt. (Oxon.), and HERBERT M. HOWE, Ph.D. Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., New York. 1955. Price, $1.85.

This slight volume, printed in typewriter offset, is the fruit of the authors' experience in teaching a course in medical terminology at the University of Wisconsin to undergraduates who expect to study medicine. Its purpose is to present, as

briefly and conveniently as possible, the most common Greek and Latin words important in medical etymology.

The authors do a thorough job. But that the presentation is as appetizing and convenient as it could be may well be challenged. If the material were presented in a single alphabetical list it would be a much more convenient work of reference than its present division permits; and the presentation of each word with bare synonyms robs the subject of much of its interest and romance. To illustrate these two criticisms: if one wishes to find the origin of "feces," one may search in vain under such reasonable headings as "Digestive system," "Physiology" or "Substances," only to find feces at last under "Body fluids"; and how much more interesting and instructive it would be to have aorta explained by something more than "lifter," or amylon by more than "starch."

To avoid the necessity for digesting Greek characters, it is all very well to transliterate into English letters; but quantities should not be sacrificed in the process —for long o, short o, long e and short e are four different letters in Greek and it is not sufficient or even accurate to substitute the English o and e without discrimination. Other inaccuracies include laevis for lēvis, smooth, on page 49, and the meaning ascribed to catheter on page 23 where it is stated to mean "that which sends down" but it of course really means the "thing that is sent down" into the bladder. Significant misprints include comes for becomes on page 23; from for form on page 61; mostos for mastos and shoulder for elbow on page 63; root for roof on page 67; and lepdoptera for lepidoptera on page 95. One also wonders why the h, an integral part of the Greek word, is parenthesized in "r(h)aphe" on page 57.

No doubt this little book is of great value to those who attend the authors' lectures. It cannot, however, be recommended unreservedly to all beginners as a stimulating introduction to what can be a most fascinating subject.

HENRY J. L. MARRIOTT

Bone and Joint X-Ray Diagnosis. By MAX RITVO, M.D., Assistant Clinical Professor of Radiology, Harvard Medical School; Instructor in Radiology, Tufts College Medical School; Lecturer on Radiology, Boston University School of Medicine; Director, Department of Radiology and Roentgenologist-in-Chief, Boston City Hospital; Associate Radiologist, Beth Israel Hospital. 752 pages; 18 × 26.5 cm. Lea and Febiger, Philadelphia. 1955. Price, $20.00.

Bone and Joint X-Ray Diagnosis is a rather comprehensive text, in which the roentgen manifestations of anomalies and diseases of bones, joints and soft tissues are discussed and evaluated. While emphasis is on the roentgen manifestations of these various lesions, important clinical aspects and diagnostic methods are adequately discussed.

The book is well written in an easy-to-read manner. The discussions of bone and joint processes are concise but present the pertinent clinical facts. While the principal lesions are illustrated with excellently reproduced radiographs, the illustrations are far less numerous than would be expected in a book of this type.

This treatise is intended primarily for radiologists and radiological residents but will prove useful as a reference to those in other specialties who are interested in the brief, pertinent aspects of bone and joint lesions.

J. M. D.

Bickham-Callander Surgery of the Alimentary Tract. Volumes I, II and III. By RICHARD T. SHACKLEFORD, M.D., Assistant Professor of Surgery, Johns Hopkins University School of Medicine; assisted by HAMMOND J. DUGAN, M.D., Assistant in Surgery, Johns Hopkins University School of Medicine. 2575 pages; 18.5 × 26 cm. W. B. Saunders Company, Philadelphia. 1955. Price, $60.00 per set.

This revision of the original Bickham text on Operative Surgery, which comprises three volumes, is an extremely comprehensive reference.

Each anatomical subdivision of the gastrointestinal tract is discussed as an individual entity, as well as from the viewpoint of its relationship to the entire tract. The surgical anatomy and physiology of each subdivision are reviewed and problems of anesthesia, incisions and post-operative care are included. Detailed descriptions of diverse operative procedures are given and an attempt is made to compare their relative merits. Diversity and the number of operative procedures described for a given area and problem are extremely inclusive.

Each volume is liberally and well illustrated and each section includes a very adequate bibliography. Each volume also contains an excellent index to the entire three volumes. This is an extremely helpful feature from the reference viewpoint.

The scope of these volumes is much more inclusive than the title implies. In addition to sections on surgery of the spleen, pancreas, biliary system, etc., there are excellent sections on the diaphragm and abdominal wall, including hiatal hernia, inguinal hernia, etc. Important contributions by well-known authorities add greatly to the value of the publication.

G. H. Y.

Color Atlas of Pathology: Endocrine System, Including Pituitary, Thyroid, Parathyroid, Adrenals and Pancreas; Gynecology and Obstetrics, Including Reproductive Organs; Breasts; Male Genital Tract; Skin. Vol. II. Prepared under auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Md. 450 pages; 18.5 × 25 cm. J. B. Lippincott Company, Philadelphia, London, Montreal. 1954. Price, $20.00.

This is the second volume of a proposed three volume set. Each systemic division is prefaced by a brief discourse on the lesions which are represented by beautifully reproduced 3 by 2⅜ color pictures. Microscopic and frequent gross aspects of the disease processes are included. Brief histories and explanatory notes accompany the illustrations.

This book is a credit to its many contributors and is commended as a guide to the student who is being introduced to pathology and to the more experienced observer who frequently requires pictorial reminders.

R. B. T.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Administrative Medicine: Transactions of the Third Conference, October 6, 7 and 8, 1954, Princeton, N. J. Edited by GEORGE S. STEVENSON, M.D., National and International Consultant, National Association for Mental Health, New York, N. Y. 172 pages; 24 × 16 cm. 1955. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.00.

Amputees and Prostheses: Report of a Conference on Prosthetics, Copenhagen, 23–28 August 1954. World Health Organization Technical Report Series No. 100. 52 pages; 24 × 16 cm. (paper-bound). 1955. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

Chlorpromazine and Mental Health: Proceedings of the Symposium Held Under the Auspices of Smith, Kline & French Laboratories, June 6, 1955, Warwick Hotel, Philadelphia, Pennsylvania. 200 pages; 23.5 × 15.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $3.00.

The Clinical Care of the Diabetic. By JAMES J. SHORT, M.D., F.A.C.P., Associate Professor of Medicine, School of Medicine, College of Medical Evangelists, etc. 84 pages; 20.5 × 13.5 cm. (paper-bound). 1955. San Lucas Press, Los Angeles. Price, $3.95.

Modern Nutrition in Health and Disease: Dietotherapy. Edited by MICHAEL G. WOHL, M.D., Chief of Human Nutrition, Division of Biological Chemistry, Hahnemann Medical College and Hospital, etc.; and ROBERT S. GOODHART, M.D., Scientific Director, The National Vitamin Foundation, Inc., etc. 1,062 pages; 24 × 15.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $18.50.

Of Research People. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine, New Orleans, Louisiana. 56 pages; 25.5 × 20.5 cm. (loose-leaf). 1955. Grune & Stratton, New York. Price, $3.00.

Pertussis in Infancy as a Cause of Behaviour Disorders in Children. (Also published as Supplement 1 to *Acta Societatis Medicorum Upsaliensis.*) By ANNA-LISA ANNELL. Statistical Analyses by ELVIR LANDER; translated from the Swedish by ERICA ODELBERG. 222 pages; 22.5 × 15 cm. (paper-bound). 1953. Almqvist & Wiksells Boktryckeri AB, Uppsala. Price, Kr. 18.

Refresher Course for Practitioners. Vol. I. (Specially Contributed Articles from the *Journal of the Indian Medical Association.*) 364 pages; 19 × 11.5 cm. 1955. Journal of the Indian Medical Association, Calcutta. Price, Rs. 8/–.

Rheumatoid Arthritis and Psoriasis Vulgaris: Internal and Cutaneous Manifestations of the Permanent Endoparasitism in the Homo Sapiens. Their Common Etiology, Pathogenesis, and Specific Vaccine Therapy. By TIBOR BENEDEK, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Stritch School of Medicine, Loyola University, etc. 308 pages; 28.5 × 22 cm. 1955. Published by the author, and distributed by Chicago Medical Book Company, Chicago. Price, $12.00.

The Treatment of Renal Failure: Therapeutic Principles in the Management of Acute and Chronic Uremia. By JOHN P. MERRILL, M.D., Associate in Medicine, Harvard Medical School and Peter Bent Brigham Hospital, etc. 238 pages; 22.5 × 14.5 cm. 1955. Grune & Stratton, New York. Price, $6.75.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1956–57

In accordance with provisions of the By-laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1956–57, are herewith announced to the Fellows and Masters of the College:

President-Elect .....Richard A. Kern, Philadelphia, Pa.
First Vice President .....Chester M. Jones, Boston, Mass.
Second Vice President .....George H. Anderson, Spokane, Wash.
Third Vice President .....Truman G. Schnabel, Sr., Philadelphia, Pa.

Regular elections will take place at the 1956 Annual Session, Los Angeles, Calif., on April 19, 1956, the date of the Annual Business Meeting, at the Shrine Auditorium, General Headquarters.

Election of nominees shall be by the Fellows and Masters. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-laws.

Respectfully submitted,
J. Murray Kinsman, Chairman, Louisville, Ky.
Fuller B Bailey, Salt Lake City, Utah
G. H. Anderson, Spokane, Wash.
Howard Wakefield, Chicago, Ill.
Thomas M. Durant, Philadelphia, Pa.

Notice of Proposed Amendment to the Constitution of the American College of Physicians

Fellows and Masters of the American College of Physicians are hereby informed that the Board of Regents has unanimously approved (Nov. 12–13, 1955) the following amendment to the Constitution of the College and will recommend its adoption at the next Annual Business Meeting at Los Angeles, Calif., April 19, 1956.

ARTICLE VI, Add Paragraph (c)

"(c)—In exceptional instances, and then only by reason of outstanding service to the cause of Internal Medicine, the Committee on Masterships may recommend to the Board of Regents for Honorary Fellowship others than members of the medical profession regardless of their nationality or residence. Such nominees may be elected to Honorary Fellowship only by the unanimous approval of the Board of Regents. Honorary Fellows elected under this provision shall not be included in those enumerated in paragraph (b) of this Article."

New Life Members

It is a pleasure for the College to announce that the following Fellows have recently become Life Members:

Dr. Prince P. Barker, Tuskegee, Ala.
Dr. Joseph F. Fazekas, Washington, D. C.
Dr. Morley J. Kert, Beverly Hills, Calif.
Dr. Edward Phillips, Los Angeles, Calif.
Dr. Duane H. Mitchel, Denver, Colo.

The names of all Life Members are inscribed in an especially prepared volume that may be examined in the College Booth during the Annual Session.

Gift to College Library of Publications by Members

The College is indeed grateful to Dr. Simon S. Leopold, F.A.C.P., Philadelphia, for presenting an autographed copy of his *Principles and Methods of Physical Diagnosis* to the College Library of Publications by Members.

Schedule of A.C.P. Coming Regional Meetings

Date	Territory	Governor	Official Guest
Feb. 17–18	PUERTO RICO, San Juan	R. Rodriguez-Molina, M.D.	Walter L. Palmer, M.D., President-Elect
Feb. 23	VIRGINIA, Charlottesville	Charles M. Caravati, M.D.	E. R. Loveland, Executive Secretary
Feb. 25	MISSOURI, Columbia	Carl V. Moore, M.D.	Philip Hench, M.D., Regent
Mar. 3	NEBRASKA, Lincoln	Edmond M. Walsh, M.D.	E. L. Bortz, M.D., 1st Vice President
Mar. 6	HAWAII, Honolulu	Nils P. Larsen, M.D.	George F. Strong, M.D., President
Mar. 23	KANSAS, Kansas City	Wm. C. Menninger, M.D.	.....
Mar. 24	SO. ILLINOIS, Springfield	C. H. Drenckhahn, M.D.	.....
Sept. 8	NORTH DAKOTA, Minot	.....	.....
Oct. 19	WESTERN NEW YORK, Albany	John H. Talbott, M.D.	.....
Oct. 27	MIDWEST, Minneapolis (Ill., Ind., Iowa, Minn., Wis.)	Wesley W. Spink, M.D.	Walter L. Palmer, M.D., President E. R. Loveland, Executive Secretary
Nov. 7	NEW JERSEY, Newark	E. C. Klein, Jr., M.D.	.....

Others scheduled but dates not yet determined include KENTUCKY-TENNESSEE at Nashville; MICHIGAN at Ann Arbor; NEW ENGLAND at Burlington, Vt.

A.C.P. Committee on Finance

Dr. A. B. Brower, Dayton, Ohio, has resigned as Chairman of the Committee on Finance of the American College of Physicians. The President has appointed as Chairman Dr. Herbert K. Detweiler, Toronto, who has previously been a member of this Committee and who is well experienced in the finances of the College. Dr. Asa L. Lincoln, New York City, has been appointed to the Committee to fill out Dr. Brower's unexpired term, to April, 1957. The other member of the committee is Dr. T. Grier Miller, Philadelphia.

Meetings, A.C.P. Committee on Credentials

The next meetings of the Committee on Credentials of the American College of Physicians will be held on March 17–18, 1956, at the College Headquarters in Philadelphia, and on April 13–14 at the Shrine Auditorium in Los Angeles. The Committee will hold its autumn meeting also in Philadelphia on Nov. 8–9, immediately preceding the meeting of the Board of Regents on Nov. 10–11.

Proposals of new members for action at these meetings must be received at the College Headquarters 60 days in advance of these dates. Governors may require that proposals be in their hands 90 days before the meetings.

The American Trudeau Society

Dr. H. Stuart K. Willis, F.A.C.P., McCain, N. C., is President of The American Trudeau Society. Other members of the American College of Physicians holding office include: Dr. David Cooper, F.A.C.P., Philadelphia, Past President; Dr. Theodore L. Badger, F.A.C.P., Boston, Vice President; Dr. William G. Childress (Associate), Valhalla, N. Y., Secretary; Dr. Julius L. Wilson, F.A.C.P., Philadelphia, Director of Medical Education Division; and Dr. Leon H. Collins, Jr., F.A.C.P., Philadelphia, Chairman of Membership Committee.

The American Trudeau Society is the medical section of the National Tuberculosis Association. Its main fields of interest are medical research and medical education. Through committee grants and publications it promotes clinical, pathological, epidemiological and other scientific studies covering the entire field of pulmonary and other thoracic diseases. Its official journal is *The American Review of Tuberculosis and Pulmonary Diseases.* Membership is open to physicians in good standing in the medical profession in the United States, Canada, and other countries. Physicians in the field of internal medicine, interested in pulmonary diseases, are welcomed. Headquarters of the Society is located at 1790 Broadway, New York 19, N. Y.

Course in Recent Advances in Internal Medicine at University of Minnesota

The University of Minnesota had a continuation course in Recent Advances in Internal Medicine at the Center for Continuation Study from Feb. 13–15, 1956, the program dealing principally with recent advances in the fields of endocrinology and metabolism, renal disease and cardiology. Dr. Cecil J. Watson, F.A.C.P., Professor and Head of the Department of Medicine, was the Director.

University of Texas Offers Four-Day Course in Cardiology

The University of Texas Postgraduate School of Medicine announces the establishment of the James J. and Una Truitt Chair in Cardiology and its sponsorship of a course in Practical Bedside Cardiology to be given by Dr. Samuel A. Levine, F.A.C.P., Clinical Professor of Medicine at Harvard Medical School, March 14–17, 1956, at Houston, Tex. Co-sponsors include the Baylor University College of Medicine and the Houston Heart Association. The course will feature the recognition and management of the most common cardiovascular problems in practice. Information may be obtained from The University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25, Tex.

Dr. Arthur M. Master, F.A.C.P., New York City, has recently concluded a series of courses, which he gave at the Mount Sinai Hospital. Subjects covered were: Elementary Electrocardiography (Jan. 16–21), Advanced Electrocardiography (Jan. 23–28), and Cardiovascular Diseases (Jan. 30–Feb. 10).

FELLOWSHIPS AND ASSISTANTSHIPS AT UNIVERSITY OF FLORIDA COLLEGE OF MEDICINE

The College of Medicine offers opportunities in 1956–57 for graduate study in the basic medical sciences, and also offers graduate work in the following fields: anatomy, biochemistry, microbiology, pathology, pharmacology and physiology. Applications must be filed not later than March 1, 1956. Additional information and the necessary forms may be obtained from Office of the Dean, University of Florida College of Medicine, Gainesville, Fla.

Dr. John T. Farrell, Jr., F.A.C.P., Philadelphia, was installed as President of the Philadelphia County Medical Society last month. Dr. Samuel B. Hadden, F.A.C.P., is the Society's President-Elect.

Dr. Samuel G. Taylor, III, F.A.C.P., Chicago, Ill., is now the official representative of the American College of Physicians on the Cancer Committee of the American College of Surgeons, succeeding Dr. Leon O. Jacobson, F.A.C.P., also of Chicago.

Dr. Harold C. Lueth, F.A.C.P., Evanston, Ill., has recently been promoted to the rank of Brigadier General in the Medical Corps, U. S. Army Reserve, by the Illinois Military District. General Lueth is currently Commanding General of the 801st Medical Center.

Dr. Joseph M. Hayman, F.A.C.P., Dean of Tufts College Medical School, Boston, has recently been appointed Chairman of the Veterans Administration Advisory Committee on Medical Research.

Dr. Robert W. Keeton, F.A.C.P., Chicago, Ill., received the F. Paul Anderson Medal awarded by the American Society of Heating and Air-Conditioning Engineers at the 62nd Annual Meeting held in Cincinnati, Ohio, Jan. 23–25, 1956. Dr. Keeton, who retired from the University of Illinois in 1951 after 26 years as Professor and Head of the Department of Internal Medicine, is the first member of the medical profession to be honored with the Society's highest award.

Dr. J. C. Geiger, F.A.C.P., Health Officer, Oakland, Calif., recently became Knight Commander, Court of Honor, of the Ancient and Accepted Scottish Rite of Freemasonry. This honor was bestowed by the Supreme Council, Washington, D. C., with the following citation: "This signal honor is bestowed in recognition of your unselfish service."

Rear Admiral Winfred P. Dana, (MC), USN, F.A.C.P., was elected President of the Association of Military Surgeons at its annual meeting held late last year. Among the Vice Presidents is Dr. Arden Freer, F.A.C.P., San Antonio, Tex., former Deputy Medical Director of the Veterans Administration.

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, has recently been chosen President-Elect of the American Roentgen Ray Society.

Dr. J. Murray Kinsman, F.A.C.P., Louisville, a regent of the College, and Dr. Franklin B. Moosnick, F.A.C.P., Lexington, have recently been appointed to the Governor's Committee on Rehabilitation. The Committee will survey the resources and needs for training the physically and mentally handicapped in Kentucky.

Newly elected officers of the Section on Gastroenterology of the Southern Medical Association include: Dr. John M. Rumball, F.A.C.P., Chairman, Coral Gables, Florida; Dr. Fred Geier, F.A.C.P., Vice Chairman, Washington, D. C.; Dr. James O. Burke, F.A.C.P., Secretary, Richmond, Va.

Dr. Rumball succeeds Dr. Charles M. Caravati, F.A.C.P., Governor for Virginia. Dr. Rumball is Chief of Medical Service, Veterans Administration Hospital, Coral Gables, and Clinical Associate Professor of Medicine, University of Miami School of Medicine. Dr. Geier is Chief of Medical Service, Doctors Hospital, Washington, and Dr. Burke is Assistant Professor of Medicine at the Medical College of Virginia.

Dr. Arthur R. Colwell, Sr., F.A.C.P., has recently been elected President of the Chicago Society of Internal Medicine. Other officers include: Dr. Fred E. Ball, Jr., F.A.C.P., Vice President, and Dr. Franklin A. Kyser, F.A.C.P., Evanston, Secretary-Treasurer.

Dr. Robert L. Richards (Associate), Chester, was recently elected Secretary of the Vermont State Medical Society.

Dr. Walter S. Priest, F.A.C.P., Chicago, was recently installed as President of the American College of Cardiology. Among the other new officers are: Dr. Simon Dack, F.A.C.P., New York City, President-Elect; Dr. Seymour Fiske, F.A.C.P., New York City, Vice President; and Dr. Philip Reichert, F.A.C.P., New York City, Secretary-Treasurer.

Dr. John A. Layne, F.A.C.P., Great Falls, was recently elected Vice President of the Montana Medical Association.

The 1955–56 officers of the Michigan Allergy Society include: Dr. Sidney Friedlaender, F.A.C.P., Detroit, President; and Dr. Kenneth P. Mathews (Associate), Ann Arbor, Vice President. Dr. Joseph H. Shaffer, F.A.C.P., Detroit, and Dr. Henry D. Beale (Associate), Toledo, Ohio, are among the members of the Executive Committee.

Dr. George K. Wever, F.A.C.P., Stockton, was elected President of the California Society of Internal Medicine at its annual meeting held late last year. Dr. William C. Mumler (Associate), Los Angeles, is Vice President, and members of the Council include Drs. Thurman K. Hill (Associate), Santa Barbara; Walter P.

Martin, F.A.C.P., Long Beach; Paul V. Morton (Associate), San Jose; Robert L. Smith, Jr., F.A.C.P., San Francisco; and James H. Thompson, F.A.C.P., San Francisco.

Current officers of the American Society of Clinical Pathologists include: Drs. Emma Sadler Moss, F.A.C.P., New Orleans, La., President; and John Lawrence Goforth, F.A.C.P., Dallas, Tex., President-Elect.

Dr. W. A. D. Anderson, F.A.C.P., Coral Gables, Fla., is President of the College of American Pathologists for 1955–56.

Current officers of the American College of Chest Physicians include: Dr. James H. Stygall, F.A.C.P., Indianapolis, President; Dr. Herman J. Moersch, F.A.C.P., Rochester, Minn., President-Elect; Dr. Burgess L. Gordon, F.A.C.P., Philadelphia, First Vice President; and Dr. Donald R. McKay, F.A.C.P., Buffalo, N. Y., Second Vice President.

Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, is President of the recently organized Society for Research on the Reticuloendothelial System, and Dr. Leon O. Jacobson, F.A.C.P., Chicago, is Vice President.

Dr. Charles C. Hillman, F.A.C.P., Miami, Fla., Executive Director of the Jackson Memorial Hospital since 1949, has recently been appointed Associate Dean of the University of Miami School of Medicine.

Dr. Frank H. Krusen, F.A.C.P., Rochester, has recently been appointed by Governor Orville Freeman to the Minnesota State Board of Health.

Dr. Samuel M. Poindexter, F.A.C.P., Boise, Idaho, former Governor of the American College of Physicians, is at present President-elect of the Academy of Psychosomatic Medicine. Dr. Wilfred Dorfman, F.A.C.P., Brooklyn, N. Y., is Chairman of the Public Education Committee and is a member of the Executive Council of the Academy.

Brig. General Elbert DeCoursey, Commandant of the Army Medical Service School, Brooke Army Medical Center, was made an honorary member of the National Society of Anatomical Pathology of Venezuela when he attended the Sixth Venezuelan Congress of Medical Scientists at Caracas, November 18–20. General DeCoursey and Dr. Lay Martin, F.A.C.P., Baltimore, Md., were the representatives of the United States.

Dr. Lewis H. Bronstein, F.A.C.P., New York City, discussed "The Employment of Individuals with Heart Disease" at a conference sponsored by the New Haven (Conn.) Heart Association on Nov. 16, 1955, as part of the Association's program of Cardiacs-in-Industry.

Dr. William P. Boger, F.A.C.P., West Point, Pa., participated in a panel discussion on "Penicillin V" at the Third Annual Symposium on Antibiotics in Washington, D. C., Nov. 3, 1955. On Nov. 9 Dr. Boger discussed "Gout and Its Therapy with Probenecid" at the Ninth Annual Postgraduate Clinic of the Michigan Academy of General Practice and the Wayne County Academy of General Practice at the Sheraton-Cadillac Hotel in Detroit.

Dr. Bernard I. Lewis, F.A.C.P., Iowa City, Iowa, addressed a meeting of the Nebraska Heart Association on Nov. 17, 1955, on "The Use of Rauwolfia Serpentina in Patients with Coronary Artery Disease and Angina Pectoris."

Drs. Howard A. Rusk, F.A.C.P., New York City, and Clark H. Millikan, F.A.C.P., Rochester, Minn., were two of the principal speakers at an open meeting of the Chicago Heart Association on Nov. 15, 1955. Their respective presentations were: "Rehabilitation in Cardiovascular Disease" and "Cerebral Atherosclerosis and the Concept of Cerebral Vasospasm."

In addition to the speakers reported in an earlier issue of this journal, Dr. Edward E. Fischel (Associate), New York City, participated in a Conference on Rheumatic Fever and Rheumatic Heart Disease, sponsored by the New York Heart Association, and held Nov. 29, 1955. His subject was "The Treatment of Rheumatic Fever and Rheumatic Carditis."

Speaking on "Chronological Age vs. Biological Age as a Basis for Retirement," Dr. Irving S. Wright, F.A.C.P., New York City, College Governor for Eastern New York, delivered one of the luncheon addresses at a conference on General Retirement Problems in Industry that was held Nov. 30, in Chicago under the joint sponsorship of the Chicago Heart Association and the Chicago Association of Commerce and Industry. On Dec. 1, Dr. Wright delivered the annual Max Ballim Memorial Lecture on Peripheral Vascular Disease at a dinner sponsored by the Sinai Hospital, Detroit.

At a Graduate Symposium on Geriatric Medicine presented by the American Geriatrics Society, Nov. 30–Dec. 1, 1955, in New York City, Dr. Walter Bauer, F.A.C.P., Boston, served as moderator for a Panel on Rheumatic Diseases; Drs. Russell L. Cecil, F.A.C.P., Richard H. Freyberg, F.A.C.P., and Charles A. Ragan, F.A.C.P., all of New York City, and Dr. Joseph Lee Hollander, F.A.C.P., Philadelphia, were participants. Dr. David C. Wilson, F.A.C.P., Charlottesville, Va., took part in a Panel on Psychological and Psychiatric Problems of Old Age.

Dr. David Salkin, F.A.C.P., San Fernando, Calif., spoke on "Bronchiectasis of the Upper Lobe" at a seminar sponsored by the West Virginia University School of Medicine, Morgantown, on Nov. 11, 1955.

Dr. Howard A. Rusk, F.A.C.P., New York City, delivered the Herzstein Lectures sponsored by the University of California School of Medicine, San Francisco, Nov. 14–16, 1955. The general theme of the Lectures was "Medicine's Number One Problem," and Dr. Rusk's specific topics were "The Dynamics and Organization of a Modern Rehabilitation," "Clinical Problems in Rehabilitation," and "The Challenge of Gerontology."

Dr. Frederick W. Williams, F.A.C.P., New York City, a Vice President of the American Diabetes Association, spoke on "Living with Diabetes" at the free public meeting conducted by the Service Unit of the Chicago Diabetes Association on Nov. 18, 1955.

Dr. J. Arthur Myers, F.A.C.P., Minneapolis, was one of the principal speakers at the 29th Annual Meeting of the American School Health Association, which met in Kansas City, Mo., Nov. 13–18, 1955. His subject was "The Association's Plan of Certification of Schools with Approved Programs for the Control of Tuberculosis."

Dr. Laurance W. Kinsell, F.A.C.P., Oakland, Calif., spoke on "Hypophysectomy in Juvenile Diabetics with Progressive Vascular Disease" at a meeting of the New England Diabetes Association in Boston on Nov. 28, 1955.

Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill., past President of the College, gave the Presidential Address at the celebration of the 40th Anniversary of the founding of the Institute of Medicine of Chicago, Dec. 6, 1955.

Dr. Henry T. Ricketts, F.A.C.P., Chicago, Ill., former President of the American Diabetes Association, discussed "The Problem of Vascular Disease in Diabetes" at a meeting of the Twin Cities Diabetes Association in Minneapolis, Minn., on Nov. 16, 1955.

At a Symposium on Tuberculosis in Childhood, presented by the National Jewish Hospital, Denver, Nov. 9–13, 1955, Dr. Walsh McDermott, F.A.C.P., New York City, spoke on "Dynamics of Antituberculous Chemotherapy."

Under the Presidency of Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich., the American Academy of Dermatology and Syphilology held its Fourteenth Annual Meeting, Dec. 3–8, 1955, in Chicago. Dr. George C. Andrews, F.A.C.P., New York City, acted as Chairman for a Panel on the Diagnosis and Treatment of Cutaneous Malignancy, and Dr. Francis E. Senear, F.A.C.P., Chicago, was Director of the Special Lectures on Endocrinology in Relation to Dermatology.

Dr. Kenneth G. Kohlstaedt, F.A.C.P., Indianapolis, was the principal speaker at a meeting on cardiovascular diseases, held by the Illinois Heart Association in conjunction with the Illinois Department of Public Health and the Sangamon County Medical Society on Dec. 1, 1955, at Springfield. He spoke on the "Management of Hypertension." Other out-of-state speakers and their topics included Dr. Paul S. Barker, F.A.C.P., Ann Arbor, Mich., "Coronary Heart Disease"; and Dr. E. Grey Dimond, F.A.C.P., Kansas City, Kans., "Instrumental Diagnosis of Heart Disease."

Among the honored guests at the 52nd Annual Assembly of the Puerto Rico Medical Association, held in Santurce, Dec. 6–10, 1955, were Drs. Bernard J. Alpers, F.A.C.P., Philadelphia, and Jerome W. Conn, F.A.C.P., Ann Arbor, Mich. Their respective topics were "The Problems of Cerebral Aneurysm" and "Clinical Implications of Aldosterone, the Newly Recognized Adrenal Steroid."

Dr. Frederic D. Zeman, F.A.C.P., New York City, discussed "Rehabilitation of the Aged" at the 35th Annual Meeting of the Association for Research in Nervous and Mental Disease, which convened in New York City, Dec. 9–10, 1955.

Dr. Paul Dudley White, M.A.C.P., Boston, delivered the keynote address at the opening of the Pennsylvania Heart Fund campaign on Jan. 30 in Philadelphia. He was introduced by Dr. Samuel Bellet, F.A.C.P., President of the Heart Association of Southeastern Pennsylvania.

After serving since July, 1951, on the staff of the Division of Medical Sciences, National Academy of Sciences—National Research Council, Dr. Leon H. Warren, F.A.C.P., joined the Clinical Investigation Department of Parke, Davis & Company in Detroit on Dec. 1, 1955.

Dr. Warren was responsible for the activities of the main Committee on Medicine and Surgery and six of the specialized advisory groups of the Division, as well as the Symposium on Atherosclerosis held by the Academy—Research Council in 1954.

Dr. Raymond F. Sheets, F.A.C.P., Iowa City, Iowa, has recently been appointed Associate Editor of *Diseases of the Chest*. He is also a member of the Council on Undergraduate Medical Education of the American College of Chest Physicians.

Dr. Walter M. Kirkendall, F.A.C.P., Iowa City, Iowa, has recently been elected to the Council of the Midwest Section of the American Federation for Clinical Research.

Dr. Walsh McDermott, F.A.C.P., New York City, has recently been appointed Director of Medical Research of the National Tuberculosis Association to succeed Dr. Esmond R. Long, F.A.C.P., Philadelphia, who retired July 1, 1955. Dr. McDermott is Editor of the *American Review of Tuberculosis and Pulmonary Diseases*.

Dr. Benjamin R. Gendel, F.A.C.P., has recently been appointed Clinical Professor of Medicine at Emory University School of Medicine, Atlanta, and Chief of Medicine at the Atlanta Veterans Administration Hospital. Dr. Gendel was formerly Chief of Medicine at the Veterans Administration Hospital (Kennedy) in Memphis, Tenn.

Dr. Charles R. Messeloff, F.A.C.P., New York City, was recently elected Director of Medicine at Lincoln Hospital.

Dr. M. Herbert Fineberg, F.A.C.P., formerly of Wilkes-Barre, Pa., has recently been appointed Manager of the Veterans Administration Hospital in East Orange, N. J.

Capt. Anton Zikmund, (MC), USN (Associate), has recently retired from the Navy after twenty years of service, and is now engaged in the private practice of internal medicine in Piedmont, Calif.

Dr. Edgar R. Miller, F.A.C.P., and his wife, Dr. Elizabeth B. Miller, Wilmington, Delaware, have joined the United Mission to Nepal, a small mountainous independent Hindu and Buddhist country on the northern border of India and the southern border of Tibet. The Christian Medical Mission, international and interdenominational, was first established in Nepal in early 1954. Nepal has a population of some 9,000,000 people with very primitive and meager medical facilities.

The Drs. Miller have provided in advance a fine medical library and their objective is directed toward setting up a medical center with good hospital facilities. Their address will be: United Medical Mission, Kathmandu, Nepal via Calcutta, India.

Coming Events

The American Medical Association will hold its 1956 Annual Meeting in Chicago, June 11–15, and the Fall Clinical Meeting will be held in Seattle, Wash., Nov. 27–30; in 1957 the Association will hold its annual convention in New York City, June 3–7.

The Fourth International Congress on Diseases of the Chest will be held in Cologne, Germany, Aug. 19–23, 1956. Additional details may be obtained from the Executive Offices of the American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.

Dr. William Dameshek, F.A.C.P., Boston, Mass., President of the International Society of Hematology, has recently announced that the Sixth Congress of the Society will be held at the Hotel Somerset in Boston the week beginning Aug. 26, 1956, and will last through Sept. 1. This is one week earlier than was originally scheduled. Additional details may be obtained from the International Society of Hematology, New England Medical Center, Harrison Ave. & Bennet St., Boston 11, Mass.

The Second International Congress of Dietetics will be held in Rome, Italy, Sept. 10–14, 1956, at the Congress Palace of Esposizione Universale Roma. The four main sections will include: recent findings of nutritional research, methods of education in nutrition, principles and problems of feeding large numbers of people, and problems of training dietitians. Additional information may be obtained from The American Dietetic Association, 620 N. Michigan Ave., Chicago 11, Ill.

The American Public Health Association, Inc., 1790 Broadway, New York 19, N. Y., has recently announced that its 84th Annual Meeting will be held in Atlantic City, N. J., Nov. 12–16, 1956. Headquarters will be at Convention Hall.

The Sixth Congress of the International Society of Geographic Pathology will be held in Paris, France, July or September, 1957. The theme of the conference will be "The Geographic Pathology of Peptic Ulcer." Plans call for a world wide study of peptic ulcer, and the International Committee in Charge of Arrangements will welcome participation by as many investigators from America as possible. Further information and questionnaire forms for the national study may be obtained from William B. Wartman, M.D., Secretary, American Section, International Society for Geographic Pathology, Northwestern University Medical School, 303 E. Chicago Ave., Chicago 11, Ill.

OBITUARIES

DR. A. A. BLAIR

Dr. Arless Arland Blair, F.A.C.P., College Governor for Arkansas, died suddenly from coronary thrombosis, Oct. 24, 1955, at a local hospital in Fort Smith.

Dr. Blair was born in Scranton, Ark., in 1891. He received his M.D. degree from the University of Tennessee College of Medicine in 1916 and interned at St. Mary's Hospital, Hoboken, N. J., 1916–17. Following his internship, he served eighteen months in the Medical Corps of the United States Army; he was discharged with the rank of Captain in 1919.

Following his military service, he began his practice in Fort Smith and at the time of his death was Head of the Department of Internal Medicine at the Cooper Clinic in Fort Smith.

Dr. Blair was a Diplomate of the American Board of Internal Medicine and was a member of the Sebastian County Medical Society, Arkansas Medical Society, American Medical Association, and American Heart Association. He became a Fellow of the College in 1927 and was made Governor for the College in 1947 and a Life Member in 1953. He was a member of the Executive Staff of the St. Edward's Mercy Hospital, Fort Smith, where he was Consulting Pathologist and Instructor to Nurses and a former Chief of Staff (1934). He was Medical Consultant to the Veterans Administration, Fayetteville, Ark., and to the United States Army Hospital at Camp Chaffee. During World War II, he served as Chairman of the Sebastian County Medical Advisory Board, Arkansas Selective Service. He had been Associate Clinical Professor of Medicine at the University of Arkansas School of Medicine since 1948.

Dr. Blair is survived by his wife, Florence McKennon Blair, 710 S. 24th St., Fort Smith, and by two daughters, Mrs. Ann Goodloe, Houston, Tex., and Mrs. George Allen, Fort Smith.

Throughout his lifetime, Dr. Blair was very active in the professional and civic life of his home town. He had a host of friends and was widely known and loved by his colleagues.

EUCLID M. SMITH, M.D., F.A.C.P.

DR. DONALD E. H. CLEVELAND

Dr. Donald Ernest Howell Cleveland, F.A.C.P., died in Vancouver, B. C., Can., on Oct. 22, 1955, after an illness of nearly two years.

Dr. Cleveland was born in Victoria, B. C., on March 10, 1890; and after his early schooling in Victoria, he entered the University of Oregon in 1908. Upon graduation in medicine from McGill University Faculty of Medicine in 1914, he interned for one year in the Royal Victoria Hospital, Montreal. He served overseas from 1916–1917 with the Royal Army Medical Corps and was with the Canadian Army Medical Corps from 1917–19. He was then Assistant Medical Advisor to the Board of Pensions Commissioners of Canada until July, 1921. Following this post, he took postgraduate training in 1922 at the Kingston Avenue Hospital, Brooklyn, and in 1923 at The New York Skin and Cancer Hospital.

In 1924, he began the practice of dermatology and syphilology in Vancouver, B. C., where he built up a very large and active practice. He was a Diplomate of The Royal College of Physicians and Surgeons of Canada. His many offices included Senior Dermatologist in the Vancouver General Hospital for 20 years, Consultant to the British Columbia Cancer Institute, Consultant to The Provincial Board

of Health, and Lecturer in the History of Medicine at the University of British Columbia Faculty of Medicine.

Dr. Cleveland was a Past President of the British Columbia Medical Association and Past President of The Catholic Doctors Guild of Vancouver. He was a Founding Fellow of The Pacific Dermatological Association. He was also a member of the Canadian Medical Association, the Canadian Dermatological Association, the Pacific Northwest Dermatological Society, the American Academy of Dermatology and Syphilology, and the British Association of Dermatology and Syphilology. He became a Fellow of the American College of Physicians in 1943 and a Life Member in 1944.

Always greatly interested in general medicine as well as in his own specialty, he took a very active part in the furthering of good medicine. He was the author of numerous medical papers and served for many years on the Publications Committee of the *Bulletin of the Vancouver Medical Association*, and was also a member of The Canadian Authors Association.

Characteristically, Dr. Cleveland, although in poor health, was giving a paper to the American Academy of Dermatology and Syphilology in Chicago, when he suffered the onset of a cerebrovascular accident, in December, 1953. His many friends in the profession and in this area will long remember his kindliness and skill.

Dr. Cleveland is survived by his widow at 5325 Connaught Dr., Vancouver, B. C., and by a son, Dr. Edward Cleveland of Winnipeg, and by a daughter, Mrs. Ivor O'Connell of Vancouver.

H. A. Des Brisay, M.D., F.A.C.P.,
Governor for British Columbia

DR. THOMAS B. CUNNANE

Dr. Thomas Bartholomew Cunnane, F.A.C.P., of Los Angeles, was born in Santa Ynez, Calif., Oct 7, 1894, and died of a coronary thrombosis Aug. 28, 1955.

He was a son of California pioneers and after graduating from Santa Barbara High School, he attended the University of Southern California, receiving his M.D. degree in 1917. He had his internship at the Los Angeles County Hospital, after which he served two years as a First Lieutenant (MC) USA in World War I. He then returned to Los Angeles and was engaged in the practice of internal medicine until the time of his death.

He was a member of the Senior Staff of the Los Angeles General Hospital, the Methodist Hospital and the Good Samaritan Hospital. He took an active interest in teaching and had been Associate Clinical Professor of Medicine at the University of Southern California School of Medicine since 1932. He was a Fellow in the Los Angeles Academy of Medicine, a member of the Los Angeles Society of Internal Medicine, and a member of the Los Angeles Heart Association. He took an active interest in the activities of the American College of Physicians and became a Fellow in 1942.

He is survived by one daughter, Colleen (Mrs. Dean Purves), and one grandchild. He is also survived by his mother, Mrs. Alice Cunnane; a sister, Mrs. Margaret Shepherd; and a brother, Dr. Philip Cunnane.

Dr. Cunnane was an excellent physician. He was a kindly man and was loved by students as well as his patients and many friends. His death is a distinct loss to Los Angeles and the American College of Physicians.

Leland Hawkins, M.D., F.A.C.P.,
Third Vice President

DR. FRED W. FITZ

Dr. Frederick William Fitz, F.A.C.P., died Oct. 8, 1955, in Chicago of coronary artery disease.

Dr. Fitz was born in Lomax, Ill., on Sept. 9, 1902. He graduated from Northwestern University Medical School in 1934. He held faculty rank at Northwestern since 1936, and at the time of his death was Associate Professor of Medicine at his alma mater. He had been Chief of the Heart and Circulation Clinic since 1950. He was an Attending Physician at Passavant Memorial Hospital and President of its Medical Staff, 1950–51.

During World War II, Dr. Fitz was a Lieutenant Colonel in the United States Army and served 34 months in the European theater.

He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1950. In Chicago he was a member of the Society of Internal Medicine and the Institute of Medicine. He held membership in the Chicago Medical Society, Illinois State Medical Society, and the American Medical Association.

Dr. Fitz was an able and enthusiastic teacher of medical students and his house staff. He was devoted to his patients. He gave them everything he had, and his patients loved him. Only a few days before his death, he had read a paper, "The Doctor and His Heart."

Dr. Fitz is survived by his widow Grace and two sons, Frederick, Jr. and Richard. Mrs. Fitz lives at 2242 Lincoln Park West, Chicago 14.

His family, friends, students, colleagues and devoted patients will miss him.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. THURMAN D. KITCHIN

The American College of Physicians, the medical profession of North Carolina, and all of us interested in medical education, suffered a great loss in the death of Thurman Delna Kitchin, M.D., F.A.C.P., on Aug. 28, 1955.

Dr. Kitchin was born Oct. 17, 1885, in Scotland Neck, N. C., the homeplace of all of the great Kitchins—Governors, Senators and Congressmen. After graduation from the Jefferson Medical College of Philadelphia in 1908, he went into general practice in Lumberton, and later returned to Scotland Neck.

In 1917, he was called to Wake Forest College as Professor of Physiology and Pharmacology, which he taught with great distinction. In 1919, he was made Dean of the School of Medicine of Wake Forest College and established its reputation of being one of the best two-year medical schools (first and second year) in this country. Those who completed the course at Wake Forest College were welcomed into the junior classes of all of the four-year medical schools.

In 1930, Dr. Kitchin became President of Wake Forest College, and greatly added to its status until his retirement in 1950. During Dr. Kitchin's presidency, he accepted the Bowman Gray gift and the income from the Smith Reynolds Fund, and with this financial support was able to move the two-year medical school from Wake Forest to Winston-Salem, and there established the four-year Bowman Gray School of Medicine of Wake Forest College, with Dr. Coy C. Carpenter as Dean.

Since its opening in 1941, the Bowman Gray School of Medicine of Wake Forest College has continued the splendid reputation which it had attained as a two-year school under Dr. Kitchin in Wake Forest.

Dr. Kitchin was elected and appointed to many offices. He was a Vice President of the Association of American Medical Colleges, President of the Medical Society of the State of North Carolina, a member of the Duke Chapter of Alpha Omega

Alpha, and of the Watauga Club in Raleigh. He also received honorary degrees from Duke and the University of North Carolina. He had been a Fellow of the American College of Physicians since 1929.

Dr. Kitchin is survived by his wife, the former Reba Calvert Clark, of Scotland Neck, and by three sons, Thurman Delna, William Walton, Chief Surgeon of the Sampson County Hospital, Clinton, N. C., and Irwin Clark, Professor of Biology at Rice Institute, Houston, Tex.

To all of us who have been fortunate enough to know him, Dr. Kitchin will always remain in our memories as an outstanding medical leader as well as a friend.

WILBURT C. DAVISON, M.D., F.A.C.P.,
Dean, Duke University School of Medicine

DR. WARREN S. LYMAN

Dr. Warren Soper Lyman, F.A.C.P., will always be remembered in Canada as the first Honorary Secretary of its Royal College of Physicians and Surgeons. He had always been interested in high standards of medical practice; and shortly after establishment of the College in 1929, he undertook responsibility for the organization of its head office in Ottawa and gave freely of his thought, time and energy in furtherance of its aims.

Dr. Lyman was born in Dubuque, Iowa, in 1876. On receiving his degree from Grinnell College, he began the study of medicine at McGill University in Montreal, graduating in 1903. He served an internship in Ottawa and took further graduate training in pathology and medicine at the Montreal General Hospital. He returned to Ottawa to practice medicine in 1908 and continued in active practice till Sept. 24, 1955, the day before his death. For almost ten years he was Pathologist to the Ottawa Protestant Hospital as well as a practicing physician. Ultimately he became Physician-in-Chief of the Ottawa Civic Hospital.

He held many offices in Canadian medical societies and for five years (1941–46) was Governor for Ontario for the American College of Physicians, having been elected a Fellow in 1929.

Dr. Lyman was a gentle, kindly man, a benevolent and trusted physician of greatest honor and integrity, and an expert fisherman. He enjoyed reading throughout his life and he was widely read.

He is survived by his widow, Mary Louis Lyman, 292 Somerset St., W., Ottawa 4.

RAY F. FARQUHARSON, M.D., F.A.C.P.,
Governor for Ontario

DR. ARTHUR ERNEST MOON, SR.

Dr. Arthur Ernest Moon, Sr., F.A.C.P. spent his entire professional life with the Scott and White Clinic of Temple, Tex. He died in that city on July 27, 1955, of a heart attack.

Dr. Moon was born in Lineville, Ala., on March 5, 1890. His college work was done at Baylor University, where he graduated in 1915. He received his M.D. degree from the University of Texas School of Medicine in 1920. He served as Associate Professor of Zoology and Physiology in Baylor University during 1915–16. After completing his internship at Scott and White Memorial Hospital, he served respectively as Associate in Internal Medicine, Internist, Head of the Medical Service and Head of the Department of Medicine at Scott and White Memorial Hospital during 1923 to 1955. He was also a Consultant in Medicine and Instructor to the Interns and Residents at the Gulf, Colorado and Santa Fe Hospital at Temple from 1943 until 1955. Between 1951 and 1955 he was Professor of Medicine at the Uni-

versity of Texas Postgraduate Medical School, Temple Division. He retired on April 1, 1955, after several years of impaired health.

Dr. Moon was a member of the Bell County Medical Society and the Texas and American Medical Associations, the Texas Heart, The Southern and Pan American Medical Associations. He was elected a Fellow of the American College of Physicians in 1937 and became a Life Member in 1946. He is survived by his wife, Mrs. Flora Wells Moon, of 716 N. 13th St., Temple.

The Board of Directors of the Scott and White Clinic expressed its esteem of Dr. Moon in this resolution:

> In the death of Doctor A. E. Moon, the staff of Scott and White Clinic has lost one of our most valuable physicians, a kindly man and a dear friend. The Board desires to express its great appreciation of these qualities and enter upon the minutes this testimony to the memory of one we loved through the years and will miss in the years to come. His rare skill and understanding and the unselfishness which enhanced these attributes made a fundamental and lasting contribution to our institution and aided to a great degree in developing better medical care for our patients.
>
> D. W. Carter, Jr., M.D., F.A.C.P.,
> Governor for Texas

DR. CHARLES SOLOMON

Dr. Charles Solomon, a Fellow of the American College of Physicians, died on Sept. 15, 1955, of Stokes-Adams disease with ventricular fibrillation.

Dr. Solomon was born in Brooklyn, N. Y., on Feb. 2, 1896. He attended the University and Bellevue Hospital Medical College and received his M.D. degree in 1918. He interned at the Jewish Hospital of Brooklyn from 1918–19 and at Montefiore Hospital from 1919–20. He was Instructor in Medicine at Long Island College of Medicine from 1929–35 and Assistant Clinical Professor of Medicine from 1935–36. He was Lecturer in Medicine at the State University of New York College of Medicine at New York City from 1952–55 and had been Director of Graduate Courses in Physiology and Pharmacology at Brooklyn College of Pharmacy of Long Island University since 1938. He became a member of the staff of Jewish Hospital in 1922, where he was formerly Chief of the Internal Medicine Clinic and Instructor in Pharmacology to the School of Nurses. He became Attending Physician at the Jewish Chronic Disease Hospital in 1934.

Dr. Solomon was the author of *Pharmacology, Materia Medica and Therapeutics* (six editions) and of *Formulary of the Jewish Hospital of Brooklyn.* He was a member of the Brooklyn Society of Internal Medicine, King's County Medical Society, Medical Society of the State of New York, and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1940. He is survived by his wife, Viva Leontine, of 51 Lefferts Ave., Brooklyn 25, N. Y.

It is with sincere regret that Dr. Solomon's many friends and confreres note his passing at this time.

Irving S. Wright, M.D., F.A.C.P.,
Governor for Eastern New York

DR. W. H. TRIMBLE

Dr. William Hugh Trimble, F.A.C.P., was born in Hogansville, Ga., Oct. 25, 1902. He died at his home in Atlanta on July 25, 1955, after an illness of several months. The cause of his death was primary bronchogenic carcinoma.

Dr. Trimble received his B.S. degree from Emory University in 1923. He then attended medical school at the University of Pennsylvania, receiving his M.D. degree in 1927. His postgraduate training was begun as an intern at Piedmont Hospital in Atlanta; he then became assistant resident and later chief resident at the Vanderbilt University Hospital in Nashville, Tenn.

By 1932 his postgraduate training had ended, and he began the practice of internal medicine in Atlanta. This continued uninterruptedly, except for his service in the U. S. Army General Hospital No. 43 (Emory Unit), from September, 1942 until January, 1946. At this time he separated from the service with the rank of Lieutenant Colonel, and he resumed practice in Atlanta which continued until November of 1954. Because of his fortitude, he continued his practice for three months after the onset of his fatal illness.

Dr. Trimble was active in teaching both at the Emory University School of Medicine and at Piedmont Hospital. He was an Associate in Medicine on the faculty at Emory University School of Medicine and at Piedmont Hospital. He was an Associate in Medicine on the faculty at Emory University Medical School. He was Visiting Physician to the Emory University Hospital, Grady Memorial Hospital, Piedmont Hospital and Georgia Baptist Hospital.

He was a Diplomate of the American Board of Internal Medicine, a member of the Fulton County Medical Society, Medical Association of Georgia, and the American Medical Association. He had been a Fellow of the American College of Physicians since 1939. He was also an enthusiastic member of the Southeastern Clinical Club, the successor organization to the old Southern Interurban Clinical Society.

In 1932 Dr. Trimble married Miss Grace Fincher, who survives him with their son and two daughters at 376 Manor Ridge Dr., N.W., Atlanta.

He is greatly missed by his family, his friends and his patients.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. FLOYD R. WRIGHT

Dr. Floyd Robbins Wright, F.A.C.P., of Townsend, Del., died Oct. 25, 1955. Born in Spencer, N. Y., in 1874, Dr. Wright received his M.D. from Cornell University Medical College in 1903, and shortly thereafter became a Physician in the Medical Department of the Clifton Springs (N. Y.) Sanitarium and Clinic. He remained here until December, 1937, when he retired from practice and moved to Smyrna, Del. Dr. Wright was elected to Fellowship in the American College of Physicians in 1921 and had been a Life Member since 1935. At one time he was a member of the Society for the Study of Internal Secretions, National Tuberculosis Association and the American Medical Association. He is survived by his wife, Alice J. Wright, Frederick Lodge, R.F.D., Townsend, Del.

TENTATIVE PROGRAM
THE AMERICAN COLLEGE OF PHYSICIANS

Thirty-seventh Annual Session

LOS ANGELES, CALIF.

April 16–20, 1956

GENERAL SESSIONS, LECTURES AND CONVOCATION

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Roger O. Egeberg

White Memorial Hospital, Los Angeles
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WELCOME TO THE CITY OF LOS ANGELES

The membership in Southern California is delighted to have this opportunity to extend a cordial welcome to you who attend the Thirty-seventh Annual Session of the American College of Physicians in Los Angeles, April 16–20, 1956.

We are proud to have been chosen as your hosts. We who are a continent removed from the Cradle of Medicine hope that you will find the Stature of Medicine in the West equal to our entertainment, a technological and cultural growth.

In keeping with the spirit of expansion which characterizes the area, we have attempted to prepare a vital program for this Session.

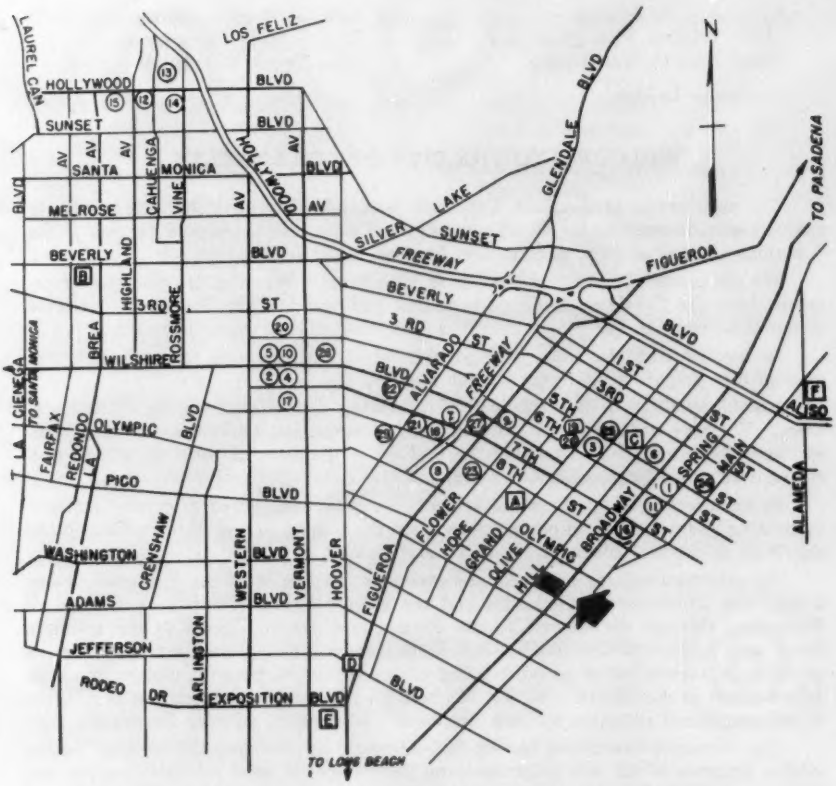
Notable, perhaps, is the technique of presenting the material for the clinical sessions. We have utilized one of our outstanding industries, television, for your comfort and convenience. To overcome the problem of distance, the sessions will be presented over closed circuits from a central studio.

In the selection of speakers and subjects, we have endeavored to present material interesting and new in an effort to stress again the coming of age of our profession in the West in medical education, research and service.

As entertainment we have planned events in keeping with the character of our living: our Philharmonic Orchestra and the Roger Wagner Chorale; a glimpse of Hollywood through the famous Moulin Rouge; our Annual Dinner at the Biltmore Bowl with Master of Ceremonies Bob Hope, known and admired not only for his professional talents but as an outstanding citizen of our community, and many of his fellow-actors as our guests. All this has been planned for your delectation in addition to our traditional reception for new members, Convocation, and the President's Ball.

The Women's Committee has worked diligently in providing the visiting women with a program which will point up those factors which make our life pleasant and interesting. The Huntington Library, the motion picture studios, our beaches and Disneyland, have all been included in a program designed to express our welcome to you who have come to join us.

It is our sincere hope that the Thirty-seventh Session will be an occasion for you to remember with pleasure and with the feeling that it has been a satisfying and worthwhile experience.



Figures 1 to 28 represent hotels. See list of hotels.

A. Embassy Auditorium
B. Pan Pacific
C. Philharmonic Auditorium
D. Shrine Auditorium & U.S.C.
E. Coliseum
F. Union Station
G. (Letter omitted on map) Moulin Rouge, Sunset Blvd. & Vine

GENERAL INFORMATION

HEADQUARTERS

Registration headquarters, the information bureau, technical and scientific exhibits, general sessions, morning lectures, clinical pathological, physiological and biochemical conferences and color televised hospital clinics, will be held at the Shrine Auditorium and Exposition Hall, 665 W. Jefferson Blvd., Los Angeles, Calif. The Los Angeles Philharmonic Orchestra—Roger Wagner Chorale Concert will also be held at the Shrine Auditorium. Meetings of Committees, of the Board of Regents, of the Board of Governors, the Convocation and the Annual Banquet will be held at the Biltmore Hotel.

HOTEL ACCOMMODATIONS

The following will be the official hotels for the session. The Biltmore and the Hilton Statler Hotels will be official hotel headquarters. An A.C.P. Housing Bureau, conducted under the Los Angeles Convention and Visitors Bureau, 1151 S. Broadway, Los Angeles 15, Calif., will handle all hotel reservations, except that the Executive Secretary will provide hotel reservations at the Biltmore Hotel for Officers, Regents, Governors and Speakers on the program. Members and guests-at-large may utilize the official reservation form accompanying the program. Additional copies of the hotel reservation form may be obtained from the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

LIST OF HOTELS

Key		For One Person	For Two Persons		Suites
			Double Bed	Twin Beds	
1	Alexandria 210 W. 5th St.	$ 4.00–$ 8.00	$ 6.00–$ 9.00	$ 7.00–$10.50	$10.00–$25.00
2	Ambassador 3400 Wilshire Blvd.	9.00– 21.00	12.00– 24.00	12.00– 24.00	25.00– 38.00
3	*Biltmore 515 S. Olive St.	5.50– 11.50	8.50– 14.50	9.00– 15.00	18.00– 33.00
4	Chancellor 3191 W. 7th St.	5.00– 8.00	8.00– 10.00	9.00– 12.00	14.00– 20.00
5	Chapman Park 3401 Wilshire Blvd.	8.00– 10.00	10.00– 12.00	12.00– 15.00	20.00– 40.00
6	New Clark 426 S. Hill St.	4.50– 7.00	6.00– 9.00	7.00– 10.00	12.00– 20.00
7	Commodore 1203 W. 7th St.	5.00– 8.00	7.50– 10.00	8.00– 11.00	20.00
8	Figueroa 936 S. Figueroa	4.50– 6.50	6.00– 8.00	7.50– 8.00	12.00– 14.00
9	Gates 830 W. 6th St.	3.50– 5.00	4.50– 6.00	5.00– 7.00	8.00– 12.50
10	Gaylord 3355 Wilshire Blvd.	7.00– 9.00	9.50– 12.50	9.50– 12.50	14.00– 22.00
11	Hayward 206 W. 6th St.	3.50– 6.00	5.00– 8.00	6.00– 9.00	10.00– 16.00
16	Lankershim 230 W. 7th St.	4.00– 5.50	5.50– 7.00	6.50– 7.50	10.50
17	Mayan 3049 W. 8th St.	3.00– 5.00	5.00– 7.00	5.50– 9.00	12.00– 15.00
18	Mayfair 1256 W. 7th St.	5.50– 9.00	7.50– 11.00	9.00– 12.00	18.50– 30.00
19	Mayflower 535 S. Grand Ave.	5.00– 7.00	5.00– 7.00	5.50– 9.00	14.50– 17.00
22	Park Wilshire 2424 Wilshire Blvd.	5.00– 7.00	6.50– 7.00	7.50– 8.50	10.00– 15.00
23	Ritz Flower 813 S. Flower St.	3.00– 4.50	4.00– 6.50	5.00– 6.50	
25	San Carlos 507 W. 5th St.	3.50– 6.00	3.50– 6.00	5.00– 7.00	7.00– 10.00
26	Savoy 601 W. 6th St.	4.50– 5.00	5.50– 6.50	6.00– 7.00	9.00– 9.50
27	*Statler Wilshire & Figueroa	6.50– 13.00	9.00– 14.00	10.00– 16.00	22.00– 34.00
28	Town House 639 Commonwealth	9.00– 17.00	14.00– 20.00	14.00– 20.00	25.00– 29.00
	Beverly Hills Beverly Hills	12.00 up	17.00 up	17.00 up	36.00 up
	Beverly Hilton Beverly Hills	12.00 up	15.00 up	15.00 up	34.00 up

* Joint Hotel Headquarters.

Who May Register—

(*a*) All members of the American College of Physicians in good standing for 1956.

(*b*) All newly elected members.

(*c*) Graduate medical students pursuing courses in local institutions of Los Angeles, without registration fee, **upon presentation of matriculation cards or other evidence of registration at these institutions**; admission to exhibits, general sessions, morning lectures, CPC's and TV Hospital Clinics.

(*d*) Members of the staff, including interns, of the Los Angeles Hospitals participating in the program, without registration fee, **upon presentation of proper identification**; admission to exhibits, general sessions, morning lectures, CPC's and TV Hospital Clinics (this does not include courtesy staff members).

(*e*) Bona fide hospital residents, regardless of their location in North America, without registration fee, **upon presentation of proper credentials from their hospitals**; admission to exhibits, general sessions, morning lectures, CPC's and TV Hospital Clinics.

(*f*) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States, Canada or Mexico, without registration fee, **upon presentation of proper credentials.**

(*g*) Qualified physicians, who may wish to attend this Session as visitors, sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee of $25.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published) included within such fee.

(*h*) Full-time medical teachers holding the rank of Assistant Professor or lower, **upon presentation of proper credentials from their medical schools,** shall be entitled to a reduction in the registration fee to $12.50.

The above regulations are essential because of the increasingly large attendance at the Annual Sessions of the College, and the necessity of accommodating members first.

Registration Bureau—While official registration will start on Monday morning, April 16, advance registration of members and exhibitors will be provided for by mail. The Registration Bureau will be set up for advance registration in the Exposition Hall of the Shrine Auditorium on Sunday, April 15, from 2:30 P.M. to 5:00 P.M. The Registration Bureau will be open throughout the week from 8:45 A.M. to 5:30 P.M.

Advance Registration of Members—In order to facilitate quick registration at the meeting for members of the College, an advance registration form, with directions, will be enclosed with the formal Program to all Fellows and Associates. The success and justification of the plan is wholly dependent upon the co-operation of members, and thus the directions should be carefully noted and the proper forms returned to the Executive Offices of the College long in advance, so that each member's envelope of forms and badge will be ready for him when he calls at the Advance Registration Window. The use of this form will eliminate long lines and delays so frequently encountered at large conventions. A member, however, should not send in this form unless he is sure he is going to be present. Last year there was a 10% "no show" of advance registrations, resulting in waste of time and material.

Registration Blanks for Panel Discussions will be enclosed with the final program to members of the College. Non-members will secure registration blanks at the Registration Bureau during the Session.

Daily Bulletins—A Daily Bulletin of registrations will be published at this meeting.

Information and Message Center—A special window at the general Registration Bureau will handle all messages, incoming telegrams and incoming mail.

Bulletin Board for special announcements will be located near the Registration Bureau.

Public Telephones—Supplementing the few public telephones in the Shrine Auditorium, a battery of public telephones will be installed in the corridor connecting the Exposition Hall and the Shrine Auditorium.

Local Transportation—Public transportation via bus or street car in Los Angeles from the various hotels to the Shrine Auditorium is inadequate, but is available. Taxis will be available, but the cost from the downtown hotels will be about $1.50 each way, and from Beverly Hills hotels about $3.00 to $4.00 each way. Arrangements have been made to provide buses, each carrying only 40 people so that each person will have a seat. The buses will shuttle from the downtown hotels to the Shrine Auditorium constantly between 8:00 A.M. and 6:00 P.M., and will provide single A.M. and P.M. trips from the Beverly Hills hotels. The total cost for this service will be $6.00 per person and will cover any number of trips desired. Tickets for this transportation may be purchased with advance registration (members only), or at the Registration Desk at the Shrine Exposition Hall, or at information booths in downtown hotels. This arrangement will provide convenience and comfort with considerable saving over taxi transportation.

Ample parking space is available at the Shrine Auditorium for those who use their own cars.

The Annual Business Meeting of the College will be held at 2:00 P.M. on Thursday, April 19, immediately preceding the afternoon General Session. All Masters and Fellows of the College are urged to be present. There will be the election of Officers, Regents and Governors and the annual reports of the Secretary-General, Executive Secretary and Treasurer. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award, the Willard O. Thompson Memorial Traveling Scholarship Award and the Mead Johnson Graduate Scholarship Awards. The President-Elect, Dr. Walter L. Palmer, Chicago, Ill., will be inducted into office. Be present and know your College!

BOARD AND COMMITTEE MEETINGS

All meetings will be held at the Biltmore Hotel, Conference Room 2, at times and places to be indicated. Special meetings will be announced and posted. A full schedule of such meetings will be published in the final program.

A **Reception and Dinner** of the members of the Board of Regents, Board of Governors, Committee Chairmen, distinguished guests, and their wives, will be held Sunday, April 15, at 7:00 P.M.; Reception in the Ballroom Foyer, followed by Dinner in the Ballroom, of the Biltmore Hotel.

A **Reception and Dinner,** tendered by Governors of the College to new Associates and Direct Fellows (elections that took place April 24, 1955, and November 12, 1955), will be held at the Biltmore Hotel, Tuesday evening, April 17, 6:30 P.M.; Reception in the Ballroom Foyer, followed by dinner in the Ballroom.

SPECIAL FEATURES

Post-Convention Tour to Hawaii—A long awaited opportunity now presents itself for an organized trip of College members to Hawaii. Governor King of Hawaii has designated the week of April 23 as the Centennial Celebration of the Hawaiian Medical Association. Dr. Nils P. Larsen, College Governor, has assisted in setting up not only a fine medical program, but an exceptionally interesting program of entertainment and sight-seeing under the best auspices.

A choice of first and tourist class reservations by United Air Lines is offered, also a choice of leaving time on Friday evening, April 20, or early Saturday morning, April 21. The planes arrive in Honolulu by Saturday morning or early evening. The Princess Kaiulani and Moana Hotels will be headquarters. The scientific programs, held in conjunction with the Hawaiian Medical Association, will be conducted as breakfast meetings from 7:30 to 10:00 A.M. at the Reef Hotel on Monday and Tuesday mornings. The entertainment features include a Luau, traditional Hawaiian feast, sight-seeing trips in and about Honolulu and the Island of Oahu, a tour to the Island of Kauai, a Pearl Harbor cruise as guests of the Naval Commandant, and many other long-to-be-remembered scenes.

The return trip may be made via the SS LURLINE, departing from Honolulu on Thursday, April 26, and arriving at Los Angeles on May 1. However, the number of available reservations on the SS LURLINE is markedly limited. Those who desire may return by United Air Lines either to Los Angeles or to San Francisco, and thus may remain a longer period in Hawaii, being able to return home at the same time as required on the SS LURLINE and with no marked increase in cost. Full and detailed information may be obtained from the Tour Conductor, Mr. Joseph P. Sims, Jr., The House of Travel, 1600 Walnut Street, Philadelphia 3, Pa. Approximately 200 reservations have already been filed; it is important that each member, anticipating making the trip, conclude his arrangements with the least possible delay. Incidentally, a member may take with him members of his family and friends.

Special Train from the East and Post-Convention Tour—A special train, originating at New York City, with special feeding trains from Cincinnati, St. Louis, Minneapolis via Omaha, joining the special train at Kansas City, has been set up by the Baltimore & Ohio Railroad, Atchison, Topeka & Santa Fe, and other railroads, leaving New York at 12:00 noon, EST, Wednesday, April 11 (Pittsburgh, 12:09 A.M., EST, April 12; Cincinnati, 9:05 A.M., EST, April 12; Minneapolis, Rock Island Lines, 11:45 A.M., CST, April 12), passing through Oklahoma, Texas, New Mexico and Arizona on April 13, stopping at the Grand Canyon of Arizona National Park on April 14, and reaching Riverside, Calif., at 8:55 A.M., PST, April 15. The group will be transferred to the famous Mission Inn at Riverside for a tour of the Inn, The Cloister and Catacombs. In the early afternoon the party will be transported to their hotels in Los Angeles by motor coach.

The group will leave Los Angeles 9:00 A.M., PST, April 21, for a three-day motor tour to San Francisco, touring through Southern California along the Pacific Ocean, visiting Santa Barbara, Santa Maria Valley, Pismo Beach, San Luis Obispo, Salinas Valley, Monterey, Santa Cruz, San Lorenzo Valley, Santa Clara Valley, with interesting stops for sight-seeing, luncheons, etc. The party will remain in San Francisco at the Sheraton Palace Hotel from Monday evening, April 23 to Wednesday morning, April 25. Comprehensive tours of the points of greatest interest in the area will be arranged. The party leaves San Francisco by special train on Wednesday evening, 9:00 P.M., PST, April 25, and will provide stops and local tours at Reno, Nev., Salt Lake City, Utah, the Royal Gorge of Colorado, Colorado Springs, and arrives at Kansas City on Monday, April 30, at 6.30 A.M., CST. At this point the various special cars will leave the special train for Cincinnati, Minneapolis and other

points, and the special train will proceed East, arriving at New York on Tuesday, May 1, in the early afternoon.

This special train has been set up particularly for those who do not elect to take the Post-Convention Tour to Hawaii. A special bulletin outlining in detail the official itinerary and giving applicable rates may be obtained from the Executive Offices of the College.

Concert, The Los Angeles Philharmonic Orchestra with The Roger Wagner Chorale and Soloists, Monday evening, April 16, 8:30 P.M., The Shrine Auditorium—The membership of Southern California proudly announces the presentation of Beethoven's Ninth Symphony by the Los Angeles Philharmonic Orchestra under the baton of Alfred Wallenstein.

The world-renowned Roger Wagner Chorale and four guest soloists will join the orchestra in this notable performance under the sponsorship of The National Drug Company of Philadelphia, Pa.

The Shrine Auditorium accommodates 6,750 guests, and despite its spaciousness, the acoustics are excellent.

The occasion is the social highlight of the Thirty-seventh Annual Session. Reserved seats will be available for Officers, Regents, Governors, distinguished guests, committee members and their ladies. Tickets of admission may be requested in advance on the application form which should be returned to the Executive Offices in Philadelphia. Tickets may also be obtained at the Registration Desk at the Shrine Auditorium on Sunday afternoon, April 15 and Monday, April 16.

YOUR NIGHT FOR FUN—Frank Sennes' Moulin Rouge, Hollywood, near Sunset Blvd. and Vine St. (Formerly Earl Carroll's Theater), Tuesday, April 17, 6:30 P.M.—The excellent cuisine and spectacular review, which have made Frank Sennes' incomparable Moulin Rouge a "must" for every visitor to the Film Capitol, provides the setting for a memorable evening of fun and fellowship. Cocktails at 6:30 P.M., with dinner and dancing, will precede the first of two ninety-minute shows featuring the famous acts and special features for which this Hollywood Night Club is famous.

The first show begins at 8:00 P.M.; the second at 10:00 P.M. The seven dollar and fifty-cent cover charge per plate (which includes tax and gratuity) is payable on admission to either show, although persons attending the later show probably will have dined previously.

Reservations may be requested in advance on the application form. At the time of the meeting reservations must be made by Tuesday, April 17, before 2:00 P.M. at the Shrine Auditorium Registration Desk.

Reception and Dinner, tendered by Governors of the College to new Associates and Direct Fellows: Biltmore Hotel, Reception in Ballroom Foyer; Dinner in Ballroom, Tuesday evening, April 17, 6:30 P.M.—The Governors of the College extend an invitation to all new Associates and Direct Fellows who were elected on April 22 and November 12, 1955, for the purpose of welcoming them to the College and to provide an opportunity to meet them personally and for them to meet the Officers and Regents of the College, as well as one another. Special invitations will be issued by mail in advance of the Annual Session. *It is urgent that the Executive Office receive acceptances, or declinations, promptly and in advance of the Annual Session.*

The Annual Convocation and President's Reception: Biltmore Hotel, Wednesday evening, April 18, 8:40 P.M.—The 1956 Annual Convocation of the College will take place in the Ballroom of the Biltmore Hotel at the time above designated. All members of the College and their families, and the Los Angeles public who are interested, are cordially invited to witness the impressive academic procession and other ceremonies. Tickets will not be required. All physicians elected Fellows of

the College since the 1955 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors, distinguished guests on the program, new Fellows to be inducted, candidates for Honorary Fellowships and Masterships, Latin-American Fellows, Traveling Scholars and Research Fellows of the College are requested to assemble in the Music Room, Biltmore Hotel, for gowning at 7:00 P.M. After gowning they will proceed to the Renaissance Room for the Pre-Convocation Assembly. The Procession will move promptly at 8:40 o'clock.

The Convocation Ceremony will include the induction of new Fellows and an address by the President of the College, Dr. George F. Strong, and the Convocational Oration, "Oscar Wilde, A Medical Appreciation," by Dr. Macdonald Critchley of London, England. The John Phillips Memorial Medal for 1956, the James D. Bruce Memorial Medal for 1956 and the Alfred Stengel Diploma for 1956 will be awarded. Masterships will be conferred on two distinguished Fellows of the College and an Honorary Fellowship upon a distinguished foreign guest. There will be present Officers or representatives of The American College of Surgeons, The American Medical Association, The Royal College of Physicians and Surgeons of Canada, The Royal College of Physicians of London, and the Royal Australasian College of Physicians.

Immediately following the Convocation, the President's Reception will be held in the Renaissance Room on the same floor as the Ballroom. Dancing will start in the Ballroom about 10:30 P.M., continuing to 1:00 A.M. Tables for individual parties will be available around the periphery of the dance floor and in the Ballroom Foyer.

The Annual Banquet: Biltmore Bowl, Thursday evening, April 19, 8:00 P.M. —At 7:00 P.M. in the Renaissance Room, there will be a "Dutch Treat" Cocktail Party to which all members and their guests are invited.

The Annual Banquet will follow at 8:00 o'clock in the beautiful Biltmore Bowl. Mr. Bob Hope will be Speaker and Master of Ceremonies. Numerous Hollywood celebrities will provide the program, details of which will be included in the special Menu-Program of the evening. Table reservations for parties of four, six and ten will be available, but to reserve a special table the individual must guarantee the exact number for the table in his party, and his party must occupy the entire table reserved.

It is anticipated that the Banquet may be so popular that the facilities of the Bowl, 1100, may be exceeded, in which case the overflow may be accommodated in the Biltmore Ballroom, to which will be televised the entire festivities. It is important that reservations be made early and tickets ($7.50) purchased at the Registration Bureau at the Shrine Exposition Hall. Tickets will be collected at the entrance to the Bowl. Only those with tickets will be accommodated. Sale of banquet tickets will close at 2:00 P.M., Wednesday, April 18, in order that adequate preparations may be concluded by the Committee.

ENTERTAINMENT OF VISITING WOMEN

The Women's Entertainment Committee in Los Angeles has planned the following program with the thought of making it attractive to all members of the family. It extends a cordial invitation to the wives and families of College Members to participate.

Certain of the entertainment features may be limited in accommodations; the Committee must make guarantees in advance in certain cases; therefore, the cooperation of all in early registration is urged. Every effort will be made to fill reservations in the order of receipt. Tickets not called for before the deadlines indicated will be released. It will help the Committee if you will return your reservation cards by March 7, and thereafter to send prompt notice of any change of plans.

Headquarters for Women's Registration will be in the Galeria Room of the Biltmore Hotel. Tickets for the tours and fashion show luncheon may be purchased there, and it will be a convenient meeting place for the women and their friends throughout the week.

Registration Hours

Sunday	2:00 P.M. to 5:00 P.M.
Monday	9:00 A.M. to 5:00 P.M.
Tuesday	9:00 A.M. to 5:00 P.M.
Wednesday	9:00 A.M. to 5:00 P.M.
Thursday	9:00 A.M. to 3:30 P.M.

Information Booths

Biltmore Hotel....Galeria Room
Statler Hotel....Ballroom Lounge
Ambassador Hotel....Lobby
Beverly Hilton Hotel....Ballroom Area

WOMEN'S PROGRAM

Sunday, April 15

2:00 P.M. to 5:00 P.M.—Registration.
Galeria Room, Entrance on North Galeria, Biltmore Hotel.

Monday, April 16

9:00 A.M. to 5.00 P.M.—Registration.
Galeria Room, Biltmore Hotel.

"WELCOME DAY." The Women's Entertainment Committee is holding "Open House" all day in the Galeria Room. We hope that as many of the women as possible will register, meet the wives of the Officers, Regents and Governors, have a cup of coffee and visit with old friends.

NEW MEMBERS: Mrs. George Strong, wife of the President of the College, will greet the wives of the men who are to be inducted at this Session, between the morning hours of ten and twelve.

1:30 to 5:00 P.M.—Tour of Hollywood, Beverly Hills and Beach.
Homes of movie stars, the Brown Derby, Hollywood Boulevard, Grauman's Chinese Theater, University of California at Los Angeles, and Pacific Ocean. Tickets, $3.00.

8:30 P.M.—Concert by The Los Angeles Philharmonic Orchestra with The Roger Wagner Chorale, Shrine Auditorium.

Tuesday, April 17

9:00 A.M. to 5:00 P.M.—Registration.
Galeria Room, Biltmore Hotel.

9:30 A.M. to 4:30 P.M.—Disneyland and Pacific Coast.
Via citrus groves, the Pacific Coast from Los Angeles Harbor to Balboa, and the Buffalo Ranch to Walt Disney's "Fabulous Magic Kingdom," with many interesting things to see and buy. Admission to Disneyland, Adults, $1.00; Children, $.50. Additional charges for special attractions. Bus trip, $3.50 (lunch not included).

9:00 A.M. to 1:00 P.M.—Television and Farmer's Market.
C.B.S. Television live broadcast (children under twelve not admitted to broadcast), a guided visit to beautiful Saint Sophia Cathedral (Greek Orthodox), MacArthur Park, and the colorful Farmer's Market. Choice of food from

fifteen different countries. Tickets, $2.25 (lunch not included). Limited to 200 each day. Tour repeated, 9:00 A.M. to 1:00 P.M., April 19 and 20.

8:00 P.M.—Moulin Rouge, Dinner and Floor Show, Hollywood.

Wednesday, April 18

9:00 A.M. to 5:00 P.M.—Registration.
Galeria Room, Biltmore Hotel.

12:30 P.M.—Luncheon and Fashion Show, Beverly Hilton Hotel, Beverly Hills. Tickets, $5.50.

8:40 P.M.—Convocation, Ballroom, Biltmore Hotel.

10:15 P.M.—President's Reception, Renaissance Room, Biltmore Hotel, followed by the President's Ball, in the Ballroom.

Thursday, April 19

9:00 A.M. to 3:30 P.M.—Registration.
Galeria Room, Biltmore Hotel.

9:00 A.M. to 1:00 P.M.—Television and Farmer's Market.
(Details on Tuesday Program.)

1:30 P.M. to 5:00 P.M.—Pasadena and Huntington Library.
The busses pass Los Angeles Civic Center, Orange Grove Avenue, the Rose Bowl, and California Institute of Technology, with visits to the Huntington Library with its noted manuscripts, paintings and sculpture, and its beautifully planted grounds with an authentic Japanese garden, and to San Gabriel Mission (Admission, $.40), fourth oldest of the California Missions, founded 1771. Tickets, $2.75.

8:00 P.M.—Annual Banquet and Film Celebrity Show in the Biltmore Bowl.

Friday, April 20

9:00 A.M. to 1:00 P.M.—Television and Farmer's Market.
(Details on Tuesday Program.)

Something New Has Been Added—Color Televised Hospital Clinics. Physicians attending the Annual Session in Los Angeles will find the color television program to be a real departure from previous colorcasts for the American College of Physicians. A number of innovations have been introduced which should prove advantageous to both participants and audience.

A moderator will be present at the auditorium who will relay questions from the audience that might be asked to clarify points in the presentations. This year, in addition to the two projection-type color receivers owned by SKF, two more projection units, contributed for the Annual Session by the American Cancer Society, will be used at the Shrine Auditorium. It will be the first time that four color receivers, each equipped with 4½ by 6-foot screens, have ever been grouped in one location for a single audience. And, presumably, that audience will be the largest ever assembled at one point to view a color television program.

At the hospital end of the colorcasts, a special film projector, supplied by CBS-TV, will enable participants to show their own color films which they have taken of cases or procedures worthy of being permanently recorded. These films will be employed to supplement other visual material and to reinforce points that otherwise could be made only verbally. This Annual Session marks the first time that film has been included in an SKF colorcast.

Through the eye of the television camera, an audience of 2500 persons is enabled to follow details of a clinical presentation as clearly as if each viewer were present in the studio with the doctor. From close-up shots of minute items, the camera can change focus and give a complete view of diagnostic and therapeutic apparatus. Thus, in the space of a few seconds, the audience views clinical material that is either too small or too large for demonstration in an orthodox platform presentation.

The clinics are designed to include a maximum amount of interesting visual material. Charts, slides, x-rays, and all other forms of graphic information pertinent to the topic under discussion are employed. The physician also benefits when patients and fellow specialists are introduced into his talk. While usually an awkward procedure on the platform, there is no difficulty before the cameras. The relative privacy of the studio in contrast to the auditorium usually makes the patient feel relaxed and more inclined to talk freely with the doctor. Should the program presenter conduct a round-table discussion with other physicians, the viewer in the audience is given what amounts to a place on the panel. Finally, the element of color lends naturalness and richness to the presentation. Many forms of illness require color to show the various pigmentation hues and shadings.

The benefits that color television brings both teacher and audience make the colorcasts at the Annual Session an important part of the scientific program—one well worth your time and attention.

About 50 individuals may be accommodated at the TV Production Studio, Room No. 1436 of the Los Angeles County General Hospital. Arrangements will be made by which tickets may be procured by those wishing to see the telecast in person. The Smith, Kline & French Laboratories, Philadelphia, have extended the courtesy of presenting the technical facilities for this portion of the program, this being the seventh year that they have provided their facilities to the College.

Medical Teaching Films—Several new medical films will be shown at the Medical Film Guild's headquarters, Booths 25–26, in the technical exhibit area. "Pitfalls in Management of Refractory Heart Failure," a motion picture film in color and sound, produced by the Medical Film Guild in collaboration with the American College of Physicians and Georgetown University Medical Center, will be shown in the main auditorium on Monday afternoon, immediately following the first General Session.

Clinical Pathological, Physiological, and Biochemical Conferences—Three types of conferences will be presented. (1) Clinical Pathological Conferences of unusual interest will be conducted by a clinician and a pathologist. The cases to be discussed have been obtained from the abundant material of the Los Angeles County General Hospital. The histories are included in the official program. We hope you will have made your diagnoses beforehand. The clinician and pathologist will invite your participation. (2) A Clinical Physiological Conference in the field of respiratory physiology will be presented by clinicians and a pathologist. Emphasis will be placed on abnormal physiology. This type of conference proved so successful at the Thirty-sixth Annual Session that the Committee has ventured into this field again. (3) A new type of conference, the Clinical Biochemical Conference, will be held. The application of the newer chemical methods and determinations will be amplified as applied to the case being discussed.

Scientific Exhibit—In the past it has been the policy of the College not to conduct a Scientific Exhibit, but to support the Scientific Exhibit of the American Medical Association, as the greatest, national Scientific Exhibit of the year. However, the Program Committee, this year, has set up a special Scientific Exhibit sponsored by the University of Southern California School of Medicine, The University of California School of Medicine at Los Angeles, The College of Medical Evangelists, The University of Oregon Medical School, Standford University School of Medicine, The University of California School of Medicine, San Francisco, The University of British

Columbia School of Medicine, The Institute for Medical Research of the Cedars of Lebanon Hospital, The Muscular Dystrophy Associations of America, The National Foundation for Infantile Paralysis and the United States Air Force through the Armed Forces Institute of Pathology.

The Scientific Exhibit will be held on the South Balcony of the Shrine Auditorium Exposition Hall. List of Exhibitors and their subjects will appear later in the final program.

The Technical Exhibit, largest in the College history, will be located on the main floor of the Shrine Exposition Hall. More than 100 firms have subscribed for 138 booths. Their exhibits will cover the wide range of interest of internists and allied specialists everywhere, and will serve as an outstanding example of the ever improving technical exhibits of the College.

The Committee on Exhibits maintains high standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation. Irrelevant exhibits are eliminated, and only firms which present a group of approved products or services of scientific interest may exhibit.

Exhibits will be open from 8:45 A.M. to 5:30 P.M. daily, Monday through Thursday, and from 8:45 A.M. to 12:45 P.M. on Friday. The Technical Exhibitors gauge the meeting by the amount of interest shown and the co-operation displayed by members of the College. The exhibits constitute a real educational program in connection with the Annual Session, and members and guests are encouraged to accord the exhibitors courteous and interested attention.

List of Technical Exhibitors

	Booth
Abbott Laboratories, North Chicago, Ill.	98–99
Adolph's Ltd., Los Angeles, Calif.	130
American Cyanamid Company, Fine Chemicals Division, New York, N. Y.	39–40
American Ferment Co., Inc., New York, N. Y.	138
Ames Company, Inc., Elkhart, Ind.	120
Armour Laboratories, The, Kankakee, Ill.	9
Association of American University Presses	60
Audio-Digest Foundation, Glendale, Calif.	132
Ayerst Laboratories, New York, N. Y.	91–92
W. A. Baum Co., Inc., Copiague, L. I., N. Y.	62
Don Baxter, Inc., Glendale, Calif.	125
Becton, Dickinson and Company, Rutherford, N. J.	13
Bilhuber-Knoll Corp., Orange, N. J.	78
Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y.	57
Bowen & Company, Inc., Bethesda, Md.	124
Boyle & Company, Los Angeles, Calif.	136
Burdick Corporation, The, Milton, Wis.	17
Burroughs Wellcome & Co. (U.S.A.), Inc., Tuckahoe, N. Y.	83
Burton, Parsons & Company, Washington, D. C.	72
Cambridge Instrument Co., Inc., New York, N. Y.	114
Carnation Company, Los Angeles, Calif.	123
Chilean Iodine Educational Bureau, Inc., New York, N. Y.	16
Ciba Pharmaceutical Products, Inc., Summit, N. J.	88
Warren E. Collins, Inc., Boston, Mass.	8
Coreco Research Corp., New York, N. Y.	137

	Booth
Dallons Laboratories, Inc., Los Angeles, Calif.	131
Davies, Rose & Company, Limited, Boston, Mass.	94
F. A. Davis Company, Philadelphia, Pa.	12
Desitin Chemical Company, Providence, R. I.	35
Devereux Schools, Santa Barbara, Calif.; Devon, Pa.	7
DeVilbiss Company, The, Somerset, Pa.	107
Doho Chemical Corporation, New York, N. Y.	4–5
Duke Laboratories, Inc., Stamford, Conn.	18
Eaton Laboratories, Norwich, N. Y.	23
Fellows Medical Manufacturing Co., Inc., New York, N. Y.	14
C. B. Fleet Co., Inc., Lynchburg, Va.	46
E. Fougera & Company, Inc., New York, N. Y.	76
Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, New York, N. Y.	77
General Electric Company, X-Ray Department, Milwaukee, Wis.	29–30
General Foods Corporation, White Plains, N. Y.	21–22, 96–97, 112–113
Gerber Products Company, Fremont, Mich.	2
Gray Pharmaceutical Company, Inc., Newton, Mass.	135
Grune & Stratton, Inc., New York, N. Y.	1
H. J. Heinz Company, Pittsburgh, Pa.	42
Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, N. Y.	90
Hoffmann-La Roche Inc., Nutley, N. J.	59
Hollister-Stier Laboratories, Los Angeles, Calif.; Chicago, Ill.; Spokane, Wash.; Philadelphia, Pa.	36
Horlicks Corporation, Racine, Wis.	122
Hyland Laboratories, Los Angeles, Calif.	28
Irwin, Neisler & Company, Decatur, Ill.	109
Ives-Cameron Company, Philadelphia, Pa.	10
Jones Metabolism Equipment Company, Chicago, Ill.	68
Lea & Febiger, Philadelphia, Pa.	15
Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.	58
Liebel-Flarsheim Company, The, Cincinnati, Ohio	41
Eli Lilly and Company, Indianapolis, Ind.	73–74–75
J. B. Lippincott Company, Philadelphia, Pa.	19
Lloyd Brothers, Inc., Cincinnati, Ohio	95
Macmillan Company, The, New York, N. Y.	51
Maltbie Laboratories Division, Wallace & Tiernan Inc., Belleville, N. J.	33
Massachusetts Indemnity Insurance Company, Boston, Mass.	34
S. E. Massengill Company, The, San Francisco, Calif.; Bristol, Tenn.	71
McNeil Laboratories, Inc., Philadelphia, Pa.	20
Mead Johnson & Company, Evansville, Ind.	93
Medco Products Company, Tulsa, Okla.	49
Medical Bureau, The, Chicago, Ill.	44
Medical Film Guild, Ltd., New York, N. Y.	25–26
Merck & Co., Inc., Rahway, N. J.	110–111

	Booth
Wm. S. Merrell Company, The, Cincinnati, Ohio	105–106
C. V. Mosby Company, The, St. Louis, Mo.	45
National Drug Company, The, Philadelphia, Pa.	47–48
Nepera Chemical Co., Inc., Yonkers, N. Y.	11
Ortho Pharmaceutical Corporation, Raritan, N. J.	139
Parke, Davis & Company, Detroit, Mich.	3
Pet Milk Company, St. Louis, Mo.	37
Pfizer Laboratories, Brooklyn, N. Y.	55–56
Purdue Frederick Company, The, New York, N. Y.	53
Riker Laboratories, Inc., Los Angeles, Calif.	66–67
Ritter Company, Inc., Rochester, N. Y.	129
A. H. Robins Company, Inc., Richmond, Va.	61
J. B. Roerig and Company, Chicago, Ill.	50
William H. Rorer, Inc., Philadelphia, Pa.	79
Sanborn Company, Cambridge, Mass.	103–104
Sandoz Pharmaceuticals, East Hanover, N. J.	52
W. B. Saunders Company, Philadelphia, Pa.	31–32
Schenley Laboratories, Inc., New York, N. Y.	6
Schering Corporation, Bloomfield, N. J.	89
Schieffelin & Co., New York, N. Y.	63
G. D. Searle & Co., Chicago, Ill.	24
Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia, Pa.	84–85–86–87
Smith, Kline & French Laboratories, Philadelphia, Pa.	69–70
Spindler & Sauppe, Los Angeles, Calif.	126
E. R. Squibb & Sons, New York, N. Y.	117–118
J. W. Stacey, Inc., San Francisco, Calif.	27
Stuart Company, The, Pasadena, Calif.; Chicago, Ill.	128
U. S. Vitamin Corporation, New York, N. Y.	80
Upjohn Company, The, Kalamazoo, Mich.	81–82
Wallace Laboratories, New Brunswick, N. J.	64–65
Warner-Chilcott Laboratories, New York, N. Y.	121
White Laboratories, Inc., Kenilworth, N. J.	54
Williams & Wilkins Co., The, Baltimore, Md.	102
Winthrop Laboratories Inc., New York, N. Y.	115–116
Woodward Medical Personnel Bureau, Chicago, Ill.	119
Wyeth Laboratories, Philadelphia, Pa.	100–101
Year Book Publishers, Inc., The, Chicago, Ill.	108
Yorke Publishing Company, Inc., The, New York, N. Y.	43

OUTLINE OF THE LOS ANGELES SESSION—APRIL 16–20, 1956

(Sessions to be held at Shrine Auditorium, Shrine Exposition Hall, and University of Southern California Campus)

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
9:00 A.M.– 1:00 P.M.	REGISTRATION VISIT YOUR EXHIBITS	T.V. Hosp. Clinics	T.V. Hosp. Clinics	T.V. Hosp. Clinics	T.V. Hosp. Clinics
9:00 A.M.–10:00 A.M.		Lecture	Lecture	Lecture	Lecture
10:00 A.M.–11:00 A.M.		Lecture	Lecture	Lecture	Lecture
11:00 A.M.–11:40 A.M.		Intermission	Intermission	Intermission	Intermission
11:40 A.M.– 1:00 P.M.		Clinical Pathological Conference	Clinical Physiological Conference	Clinical Biochemical Conference Clinical Pathological Conference	Clinical Pathological Conference Clinical Pathological Conference
11:50 A.M.– 1:10 P.M.		Panels (5)	Panels (5)	Panels (4)	Panels (4)
2:00 P.M.– 3:10 P.M.	1st General Session	2nd General Session	3rd General Session	Ann. Bus. Meeting 4th General Session	5th General Session
3:10 P.M.– 3:50 P.M.	Intermission	Intermission	Intermission	Intermission	Adjournment, 3:45 P.M.
3:50 P.M.– 5:00 P.M.	1st General Session Continued	2nd General Session Continued	3rd General Session Continued	4th General Session Continued	
8:00 P.M.		Light Entertainment Moulin Rouge, Hollywood (By Reservation) Shows, 8:00 & 10:00		Film Celebrity Show and Dinner Biltmore Bowl (By Reservation) (Black Tie)	
8:30 P.M.	L.A. Philharmonic Orchestra and Roger Wagner Choral Group Shrine Auditorium (Black Tie)		Convocation and President's Reception and Dance Biltmore Ballroom Music by U.S.C. School of Music (Black Tie)		

GENERAL SESSIONS PROGRAM

Shrine Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 16, 1956

Presiding Officer

George C. Griffith, F.A.C.P., Los Angeles
General Chairman

P.M.

2:00 **Invocation:**
The Rt. Reverend FRANCIS ERIC BLOY, D.D., S.T.D.
Bishop of Los Angeles (Episcopal).

Addresses of Welcome:
The Honorable NORRIS POULSON
Mayor of the City of Los Angeles.
EDWARD C. ROSENOW, JR., F.A.C.P.
President, Los Angeles County Medical Association.
FRED D. FAGG, JR., J.D., LL.D.
President, University of Southern California.

Response to Addresses of Welcome.
GEORGE F. STRONG, F.A.C.P., F.R.C.P. (Lond.), F.R.C.P. (C), Vancouver, B. C.
President, The American College of Physicians.

Presiding Officer

George F. Strong, F.A.C.P., President

2:20 **The Importance of the Fractional Serum Bilirubin in Clinical Medicine.**
CECIL J. WATSON, F.A.C.P., Minneapolis.
Professor of Medicine, University of Minnesota Medical School.

2:40 **Modern Treatment of the Malabsorption Syndrome.**
KEITH J. R. WIGHTMAN, F.A.C.P., Toronto.
Associate Professor of Medicine and Therapeutics and Head of the Department of Therapeutics, University of Toronto Faculty of Medicine.

3:10 INTERMISSION.

Presiding Officer

Edward L. Bortz, F.A.C.P., Philadelphia
First Vice President, A.C.P.

3:50 **Recent Advances in the Diagnosis and Treatment of Systemic Lupus Erythematosus.**
EDMUND L. DUBOIS, (Associate), Los Angeles.
Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

4:05 **Observations on the Pathogenesis, Course and Treatment of Non-obstructive Pyelonephritis.**
HENRY D. BRAINERD, SR., F.A.C.P., San Francisco.
William Watt Kerr Professor of Clinical Medicine, University of California School of Medicine.

LEE M. CECIL, M.D., (by invitation), San Francisco.
Fellow in Medicine, University of California School of Medicine.

4:20 **The Importance of a Regimen of Diet Therapy, a High Fluid Intake and Other Measures Adjuvant to Hormonal Therapy in the Nephrotic Syndrome.**
JOHN A. LAYNE, F.A.C.P., and F. R. SCHEMM, F.A.C.P. (deceased), Great Falls.
Department of Medicine, Great Falls Clinic and the Metabolic Unit of Montana Deaconess Hospital.

4:35 **Unusual Features of Severe Aortic Insufficiency and Criteria for Operation.**
W. PROCTOR HARVEY, M.D., (by invitation), Washington.
Assistant Professor of Medicine and Director of the Heart Station, Georgetown University School of Medicine.

4:50 ADJOURNMENT.

5:00 **Elective: "Pitfalls in Management of Refractory Heart Failure."**
A motion picture film in color and sound—35 minutes. Produced by Medical Film Guild in collaboration with The American College of Physicians and Georgetown University Medical Center.

SECOND GENERAL SESSION

Shrine Auditorium

Tuesday Afternoon, April 17, 1956

Presiding Officer

Cyrus C. Sturgis, F.A.C.P., Ann Arbor
Regent and Past President, A.C.P.

P.M.

2:00 **Experiences with Transplants of Cultured Parathyroid Tissue in Hypoparathyroidism.**
ROBERTO F. ESCAMILLA, F.A.C.P., San Francisco.
Associate Clinical Professor of Medicine, University of California School of Medicine.
LEON GOLDMAN, F.A.C.S., (by invitation), San Francisco.
Professor of Surgery, University of California School of Medicine.
GILBERT S. GORDAN, JR., F.A.C.P., San Francisco.
Assistant Professor of Medicine, University of California School of Medicine.
C. HENRY KEMPE, M.D., (by invitation), San Francisco.
Assistant Professor of Pediatrics, University of California School of Medicine.

2:20 **The James D. Bruce Memorial Lecture on Preventive Medicine: Remarks on the Present Status of Etiologic Discovery in Human Viral Diseases.**
JOHN F. ENDERS, Ph.D., Sc.D., (by invitation), Boston.
Associate Professor of Bacteriology and Immunology, Harvard Medical School; Chief, Research Division of Infectious Diseases, The Children's Medical Center.

2:50 **Constitutional Insensitivity to Pain.**
MACDONALD CRITCHLEY, F.R.C.P. (Lond.), (by invitation), London, England.
Senior Neurologist, Kings College Hospital; Physician, National Hospital Queen Square; Consulting Neurologist to the Royal Navy.

3:10 INTERMISSION.

Presiding Officer

Edward C. Reifenstein, Sr., F.A.C.P., Syracuse
Second Vice President, A.C.P.

3:50 **A Thrombasthenic Syndrome Associated with Hyperheparinemia.**
WARREN N. BELL, M.D., (by invitation), Jackson.
Associate Professor of Medicine and Director of Laboratories, University of Mississippi School of Medicine.
IRVING IMBER, F.A.C.P., Reading.
Assistant Instructor in Medicine, University of Pennsylvania School of Medicine.

4:05 **Aldosterone and Arterial Hypertension.**
JACQUES GENEST, F.A.C.P., Montreal.
Director, Clinical Research Department, Hotel Dieu Hospital.

4:20 **Some Quantitative Aspects of Quinidine Therapy.**
MAURICE SOKOLOW, F.A.C.P., San Francisco.
Associate Professor of Medicine, University of California School of Medicine.

4:35 **Modification of Abnormal Serum Lipid Patterns in Atherosclerosis by the Administration of Sitosterol.**
MAURICE M. BEST, JR., F.A.C.P., Louisville.
Assistant Professor of Medicine, University of Louisville School of Medicine.
CHARLES H. DUNCAN, M.D., (by invitation), Louisville.
Assistant Professor of Medicine and Associate in Psychiatry, University of Louisville School of Medicine.

4:50 ADJOURNMENT.

THIRD GENERAL SESSION

Shrine Auditorium

Wednesday Afternoon, April 18, 1956

Presiding Officer

Howard P. Lewis, F.A.C.P., Portland, Ore.

P.M.
2:00 **Observations on Altered Purine Metabolism in Experimental Porphyria.**
ROBERT A. ALDRICH, M.D., (by invitation), Portland, Ore.
Associate Professor of Pediatrics, University of Oregon Medical School.

2:20 **The John Phillips Memorial Lecture: The Nature of Molecular Diseases.**
LINUS PAULING, Sc.D., Ph.D., (by invitation), Pasadena.
Professor of Chemistry, California Institute of Technology.

2:50 **Chronic Bronchitis and Emphysema.**
RONALD V. CHRISTIE, M.D., F.R.C.P. (C. & Lond.), (by invitation), Montreal.
Professor of Medicine, McGill University Faculty of Medicine.

3:10 INTERMISSION.

Presiding Officer

Leland Hawkins, F.A.C.P., Los Angeles

3:50 **Actinomycosis: Some Concepts of Therapy and Prognosis.**
JOHN COLLINS HARVEY, (Associate), Baltimore.
Assistant Professor of Medicine, The Johns Hopkins University School of Medicine.

4:05 **Intermittent Cerebrovascular Ischemia and Its Treatment.**
CLARK H. MILLIKAN, F.A.C.P., Rochester, Minn.
Associate Professor of Neurology, University of Minnesota (Mayo Foundation); Consultant in Neurology, Mayo Clinic.
ROBERT G. SIEKERT, M.D., (by invitation), Rochester, Minn.
Consultant in Neurology, Mayo Clinic.

4:20 **The Fractionation of Important Constituents of Gastric Juice other than Hydrochloric Acid.**
STEWART G. WOLF, JR., F.A.C.P., Oklahoma City.
Professor of Medicine and Head of the Department, University of Oklahoma School of Medicine.
Co-Authors: RANWEL CAPUTTO, M.D., VIRGINIA RICHMOND, M.S., and PHILLIP C. JOHNSON, M.D., (all by invitation).

4:35 **The Diagnostic, Prognostic, and Epidemiologic Significance of SGO—Transaminase Alterations in Acute Hepatitis.**
FELIX WROBLEWSKI, F.A.C.P., New York.
Instructor in Medicine, Cornell University Medical College; Assistant Attending Physician, Memorial Center for Cancer and Allied Diseases.
JOHN S. LADUE, F.A.C.P., New York.
Assistant Clinical Professor of Medicine, Cornell University Medical College; Associate Attending Physician, Memorial Center for Cancer and Allied Diseases.

4:50 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 18, 1956

8:40 o'Clock

Ballroom, Biltmore Hotel

LEMUEL C. MCGEE, Marshal

Fellows to be inducted, Officers, Regents, Governors, Distinguished Guests, and Recipients of Awards; Gowning, 7:00 P.M., Music Room; Pre-Convocation Assembly, 7:45 P.M., Renaissance Room.

All members of the profession and the general public are cordially invited.

1. Processional.
2. The President's Address.
   GEORGE F. STRONG.
3. Conferring of Fellowships by the President.
4. Conferring of Masterships by the President.
5. Conferring of Honorary Fellowship by the President.
6. Presentation of the John Phillips Memorial Medal for 1956.
7. Presentation of the James D. Bruce Memorial Medal for 1956.
8. Presentation of the Alfred Stengel Memorial Award for 1956.
9. The Convocational Oration: "Oscar Wilde, A Medical Appreciation."
   MACDONALD CRITCHLEY, M.B., Ch.B., M.D., F.R.C.P. (Lond.), London, England.
10. Recessional.

The President's Reception will follow in the Renaissance Room at 10:30 o'clock. The audience is requested to vacate the Ballroom temporarily while the room is reset for Dancing. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Shrine Auditorium

Thursday Afternoon, April 19, 1956

Presiding Officer

George F. Strong, F.A.C.P., President

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award, the Willard O. Thompson Memorial Traveling Scholarship Award and the Mead Johnson Postgraduate Residency Scholarship Awards. Reports will be received from the Secretary-General, Executive Secretary and Treasurer; an amendment to the Constitution and By-Laws will be presented; elections of new Officers, Regents and Governors will take place; President-Elect Walter L. Palmer, of Chicago, Ill., will be inducted as President and will make a brief inaugural address.

Presiding Officer

Walter L. Palmer, F.A.C.P., Chicago

2:30 Bedside Methods for Studying a Patient for Peripheral Vascular Diseases.
GEORGE E. BURCH, F.A.C.P., New Orleans.
Henderson Professor of Medicine and Chairman of the Department, Tulane University Unit, Charity Hospital of Louisiana at New Orleans.

2:50 The Clinical Significance of the Elastic Properties of the Lung.
RICHARD V. EBERT, F.A.C.P., Little Rock.
Professor of Medicine and Head of the Department, University of Arkansas School of Medicine.

3:10 INTERMISSION.

Presiding Officer

Dwight L. Wilbur, F.A.C.P., San Francisco

3:50 **Temporal Arteritis: A Focal Localization of a Systemic Disease—Report of 105 Cases.**

BAYARD T. HORTON, F.A.C.P., Rochester, Minn.
Head of a Section in Division of Medicine, Mayo Clinic.

THOMAS B. MAGATH, F.A.C.P., Rochester, Minn.
Professor of Clinical Pathology and Parasitology, University of Minnesota (Mayo Foundation); Chief, Division of Clinical Pathology and Biochemistry, Mayo Clinic.

4:05 **Survival in Untreated and Treated Cancer.**

MICHAEL B. SHIMKIN, F.A.C.P., Bethesda.
Chief, Biometry and Epidemiology Branch, National Cancer Institute, Department of Health, Education and Welfare.

M. H. GRISWOLD, M.D., (by invitation), Hartford.
Chief, Division of Cancer and Other Chronic Diseases, Connecticut State Department of Health.

4:20 **Normal and Abnormal Levels of Blood Cortisol.**

PHILIP S. HENCH, F.A.C.P., Rochester, Minn.
Professor of Medicine, University of Minnesota (Mayo Foundation); Senior Consultant and Head of Section on Rheumatic Diseases, Mayo Clinic.

4:35 **Differential Diagnosis of the Pain of Coronary Heart Disease.**

A. CARLTON ERNSTENE, F.A.C.P., Cleveland.
Chief of Staff, Division of Medicine, Cleveland Clinic.

4:50 ADJOURNMENT.

Thursday Evening, April 19, 1956

7:00 o'Clock

Renaissance Room, Biltmore Hotel

"DUTCH TREAT" COCKTAIL PARTY

8:00 o'Clock

Biltmore Bowl

THE ANNUAL BANQUET OF THE COLLEGE
and
FILM CELEBRITY SHOW

Master of Ceremonies

BOB HOPE

Procure tickets at the Registration Bureau, Shrine Auditorium, Exposition Hall, before 2:00 P.M., Wednesday. Arrangements may be made for table reservations for 4, 6, or 10 only. The person reserving table must guarantee its full occupation. The Biltmore Bowl will accommodate about 1,100; the overflow may be accommodated in the Biltmore Ballroom to which will be televised the entire proceedings.

FIFTH GENERAL SESSION

Shrine Auditorium

Friday Afternoon, April 20, 1956

Presiding Officer

Stacy R. Mettier, F.A.C.P., San Francisco

Governor for Northern California and Nevada, A.C.P.

P.M.

2:00 **The Selective Localization of Porphyrin in Malignant Tumors and Its Significance in Relation to Radiosensitivity.**

SAMUEL SCHWARTZ, M.D., (by invitation), Minneapolis.
Associate Professor of Experimental Medicine, University of Minnesota Medical School.

KAREL ABSOLON, M.D., (by invitation), Minneapolis.
American Cancer Fellow, Department of Surgery, University of Minnesota Medical School.

HALVOR VERMUND, M.D., (by invitation), Minneapolis.
Assistant Professor, Department of Radiology, University of Minnesota Medical School.

2:20 **The Lilly Lecture: Diabetes Mellitus and Clinical Research.**

EWEN DOWNIE, F.R.A.C.P., Melbourne, Australia.
Senior Honorary Physician and Dean of the Clinical School, Alfred Hospital, University of Melbourne.

2:50 **Seven Years' Experience with a Low Fat Diet in Multiple Sclerosis.**

ROY L. SWANK, M.D., (by invitation), Portland, Ore.
Professor of Neurology and Head of the Division, University of Oregon Medical School.

3:10 **Fat Embolism: a Problem of Increasing Importance to the Internist and Orthopedist.**

JULIAN LOVE, F.A.C.P., Corona.
Captain, (MC), U.S.N., Commanding Officer, U. S. Naval Hospital.

WILLIAM S. STRYKER, M.D., (by invitation), Corona.
Commander, (MC), U.S.N., Chief of Orthopedic Service, U. S. Naval Hospital.

3:25 **Analgesic Properties of Mixtures of Chlorpromazine with Morphine and Meperidene.**

GEORGE L. JACKSON, (Associate), Harrisburg.
Associate in the Department of General Medicine and Co-Chairman, Department of Radioactive Isotopes, Harrisburg Polyclinic Hospital.

3:40 ADJOURNMENT.

GENERAL SESSIONS

To be read if time permits

Factors in the Stomach Important to General Metabolism.

DONALD C. BALFOUR, JR., (Associate), Los Angeles.
Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

Prednisone and Prednisolone in the Practical Management of Rheumatic Diseases.

EDWARD W. BOLAND, F.A.C.P., Los Angeles.
Chairman, Department of Medicine, St. Vincent's Hospital.

Four-Minute Limit for Cardiac Resuscitation.

SEYMOUR L. COLE, F.A.C.P., Beverly Hills.
Assistant Clinical Professor of Medicine, University of Southern California School of Medicine.

ELIOT CORDAY, (Associate), Beverly Hills.
Instructor in Medicine, University of California School of Medicine at Los Angeles.

I^{131} and other Anti-Thyroid Drugs Beneficial in the Treatment of Supraventricular Tachycardia in the Euthyroid Patient.

ELIOT CORDAY, (Associate), Beverly Hills.
Instructor in Medicine, University of California School of Medicine at Los Angeles.

HERBERT GOLD, LAURO B. DE VERA and HENRY JAFFE, (all by invitation).

The Chemical Determination of Adrenalin-like Substances in Urine in the Differential Diagnosis of Essential Hypertension and Pheochromocytoma.

RICHARD J. HENRY, (by invitation), Los Angeles.
Assistant Professor of Clinical Medicine, University of Southern California School of Medicine.

CHARLES SOBEL, B.S., (by invitation).

Post-Menopausal Adrenal Insufficiency as the Cause of Climacteric Syndrome.

PAUL STARR, F.A.C.P., Pasadena.
Professor of Medicine and Co-Head of Research, Department of Medicine, University of Southern California School of Medicine.

Anticoagulant Therapy and its Pitfalls.

ARNOLD G. WARE, Ph.D., (by invitation), Los Angeles.
Associate Professor of Biochemistry and Nutrition, University of Southern California.

ROBERT STRAGNELL, (by invitation), Los Angeles.
Instructor in Medicine, University of Southern California School of Medicine.

The Chemistry of the Elastic Changes in the Aorta.

HANS H. ZINSSER, (by invitation), Los Angeles.
Assistant Professor of Surgery (Urology), University of Southern California School of Medicine.

MORNING LECTURES

There are Lectures daily, 9:00 A.M. to 11:00 A.M., Tuesday through Friday. These are intended to be "teaching lectures," which enable the speakers to cover their subjects rather completely and to illustrate them adequately.

Tuesday, April 17, 1956

Shrine Auditorium

Presiding Officer

Herbert K. Detweiler, F.A.C.P., Toronto

A.M.

9:00 **Recent Advances in the Laboratory Diagnosis of Virus Infections.**

ANDREW J. RHODES, F.R.C.P. (Edin.), (by invitation), Toronto.
Professor of Virus Infections, University of Toronto School of Hygiene; Director of The Research Institute, Hospital for Sick Children.

10:00 **Acute Coronary Insufficiency—Its Differential Diagnosis and Treatment.**

ARTHUR M. MASTER, F.A.C.P., New York.
Associate Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons.

HARRY L. JAFFE, M.D., (by invitation), New York.
Assistant Attending Physician in Cardiology, Mt. Sinai Hospital.

LEONARD E. FIELD, (Associate), New York.
Research Assistant in Cardiology, Mt. Sinai Hospital.

11:00 ADJOURNMENT.

Wednesday, April 18, 1956

Presiding Officer

Richard A. Kern, F.A.C.P., Philadelphia
Secretary General, A.C.P.

9:00 **Current Concepts of the Nature and Pathogenesis of Essential Hypertension.**

KENNETH A. EVELYN, F.A.C.P., Vancouver.
Professor of Experimental Medicine, University of British Columbia School of Medicine; Director of the British Columbia Medical Research Institute.

9:40 **The Physiology of the Adrenal Cortex in Man and Some Recent Applications to the Clinical Field.**

PETER H. FORSHAM, M.D., (by invitation), San Francisco.
Associate Professor of Medicine and Pediatrics, and Director of Metabolic Unit for Research in Arthritis and Allied Diseases, University of California Medical Center.

VINCENT C. DIRAIMONDO, M.D., (by invitation), San Francisco.
Assistant Research Physician, Departments of Medicine and Pediatrics, and the Metabolic Unit for Research in Arthritis and Allied Diseases, University of California Medical Center.

10:20 **Basic Principles in the Chemotherapy of Tuberculosis.**
ROBERT H. EBERT, F.A.C.P., Chicago.
Professor of Medicine, University of Chicago, The School of Medicine; Consultant, Chicago State Tuberculosis Sanitarium.

11:00 ADJOURNMENT.

Thursday, April 19, 1956

Shrine Auditorium

Presiding Officer

Donald C. Balfour, Jr., (Associate), Los Angeles

A.M.

9:00 **The Use of Tissue Culture Methods in Experimental Medicine.**
C. M. POMERAT, M.D., (by invitation), Galveston.
Professor of Cytology, University of Texas Medical Branch.

10:00 **Biological Comparison of Adult, Embryonic, and Cancer Tissue.**
HARRY S. N. GREENE, M.D., (by invitation), New Haven.
Anthony N. Brady Professor of Pathology and Chairman of the Department of Pathology, Yale University School of Medicine.

11:00 ADJOURNMENT.

Friday, April 20, 1956

Presiding Officer

Edward C. Rosenow, Jr., F.A.C.P., Los Angeles

9:00 **Current Problems in the Management of Staphylococcal Infections.**
DAVID E. ROGERS, M.D., (by invitation), New York.
Assistant Professor of Medicine and Head of the Division of Infectious Disease, Cornell University Medical College.

10:00 **Neurosurgical Alleviation of Parkinsonism, Chorea and Athetosis (Illustrated by moving pictures).**
IRVING S. COOPER, F.A.C.S., (by invitation), New York.
Assistant Professor of Neurologic Surgery, New York University College of Medicine; Director, Department of Neurosurgery, St. Barnabas Hospital; Associate Attending Neurosurgeon, University and Bellevue Hospitals.

11:00 ADJOURNMENT.

CLINICAL PATHOLOGICAL CONFERENCES, CLINICAL PHYSIOLOGICAL CONFERENCE, AND CLINICAL BIOCHEMICAL CONFERENCE

The accompanying table gives the schedule of these Conferences. The cases, omitting the illustrations, appear on the following pages.

Qualified men have been selected as clinicians and pathologists.

A new feature of this program is a Clinical Biochemical Conference, Thursday morning, April 19, 11:40 A.M. to 12:20 P.M.

In connection with the Clinical Pathological Conferences, members are encouraged to make their own diagnoses in advance. The protocols will be discussed by the

CLINICAL PATHOLOGICAL CONFERENCES, CLINICAL PHYSIOLOGICAL CONFERENCE, AND CLINICAL BIOCHEMICAL CONFERENCE

Shrine Auditorium

	Tuesday, April 17, 1956	Wednesday, April 18, 1956	Thursday, April 19, 1956	Friday, April 20, 1956
11:40 A.M. to 12:20 P.M.	**Clinical Pathological Conference** **Clinician** Carl V. Moore, F.A.C.P., Busch Professor of Medicine, Washington University School of Medicine, St. Louis. **Pathologist** John W. Budd, (by invitation), Associate Clinical Professor of Pathology, University of Southern California School of Medicine, Los Angeles.	**Clinical Physiological Conference** **Clinician** Roger H. L. Wilson, (Associate), Clinical Instructor in Medicine, University of California School of Medicine, San Francisco. **Clinician** Hurley L. Motley, (by invitation), Professor of Medicine, University of Southern California School of Medicine; Director, Cardio-Respiratory Laboratory; Los Angeles. **Pathologist** L. John Tragerman, (by invitation), Clinical Professor of Pathology, University of Southern California School of Medicine, Los Angeles.	**Clinical Biochemical Conference** (First Case) **Clinician** Clement A. Finch, (by invitation), Associate Professor of Medicine, University of Washington School of Medicine, Seattle. **Pathologist** Albert F. Brown, (by invitation), Associate Professor of Pathology, College of Medical Evangelists; Pathologist, Glendale Sanitarium and Hospital, Los Angeles.	**Clinical Pathological Conference** (First Case) **Clinician** Cecil J. Watson, F.A.C.P., Professor of Medicine and Head of the Department, University of Minnesota Medical School, Minneapolis. **Pathologist** Hugh A. Edmondson, (by invitation), Professor of Pathology and Head of the Department, University of Southern California School of Medicine, Los Angeles.
12:20 P.M. to 1:00 P.M.			**Clinical Pathological Conference** (Second Case) **Clinician** Donald W. Petit, (by invitation), Associate Professor of Medicine, University of Southern California School of Medicine, Los Angeles. **Pathologist** Orlyn B. Pratt, F.A.C.P., Professor of Pathology, College of Medical Evangelists, Los Angeles.	**Clinical Pathological Conference** (Second Case) **Clinician** William N. Valentine, (by invitation), Associate Professor of Medicine, University of California School of Medicine at Los Angeles. **Pathologist** L. J. Zeldis, (by invitation), Professor of Pathology, University of California School of Medicine at Los Angeles.

clinicians, who are expected to make the correct diagnoses, and, perhaps, criticize the treatment. The post-mortem findings, their interpretation and their integration with the clinical aspects will then be presented by the pathologist, in whose department the case was autopsied. Moderators and conference personnel will answer questions that may arise, as time permits.

No special tickets required, other than general registration badge.

PANEL DISCUSSIONS

Topics of intimate interest and practical value to all members of the College have been chosen. Qualified men have been selected as Moderators and Panelists. All Panels are scheduled from Tuesday through Friday, from 11:50 A.M. to 1:10 P.M., at places indicated on the following chart.

Tickets will be required for certain Panels as indicated in the headings of the chart. Where capacities are limited, admission by ticket will be enforced. Applications for tickets to Panels may be made in advance by MEMBERS on a regular application form which will accompany the final program. Tickets will also be available at the Registration Bureau, Shrine Auditorium. NON-MEMBERS may not register for Panels by mail, but should secure their tickets directly at the Registration Bureau at the meeting.

Members may submit in writing three weeks before the Session, through the Executive Secretary of the College, questions concerning any phase of the subjects listed. The application form for tickets will also provide space on which to fill in these questions. Moderators and Panelists will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions, including questions from the floor, as time permits.

A new feature of the program is the publication, following the chart, of brief reviews of the problems under discussion.

PANEL DISCUSSIONS
UNIVERSITY OF SOUTHERN CALIFORNIA CAMPUS

	Bovard Auditorium (Admission by badge; no tickets)	Founders Hall Conference Room A (Admission by ticket only)	Founders Hall Conference Room B (Admission by ticket only)	Founders Hall Conference Room C (Admission by ticket only)	Founders Hall Conference Room D (Admission by ticket only)
Capacity	1500	350	350	170	170
Tuesday April 17 11:50 A.M. to 1:10 P.M.	P-1 **Aneurysms of the Aorta and Segmental Occlusion of the Aorta, Iliac Arteries and Femoral Arteries** Moderator *Edgar V. Allen Rochester Michael E. DeBakey Houston Charles T. Dotter Portland Davitt A. Felder St. Paul *Irving S. Wright New York	P-2 **Infections of the Gastrointestinal Tract** Moderator *William A. Sodeman Columbia Hamilton H. Anderson San Francisco H. W. Brown New York Rodney C. Jung New Orleans	P-3 **Clinical Endocrinology for the Internist** Moderator *Roberto F. Escamilla San Francisco *Hans Lisser San Francisco *E. Perry McCullagh Cleveland *Paul Starr Los Angeles *Donald R. Wilson Edmonton	P-4 **Newer Aspects in the Management of Rheumatoid Arthritis** Moderator *William D. Robinson Ann Arbor *Edward W. Boland Los Angeles *Ephraim P. Engleman San Francisco *Charley J. Smyth Denver	P-5 **Hypersensitivity Mechanisms** Moderator *Robert H. Ebert Chicago Robert Good Minneapolis Sidney Raffel Palo Alto
Wednesday April 18 11:50 A.M. to 1:10 P.M.	P-6 **Recent Advances in the Field of Corticoids and their Application to Therapy** Moderator Peter H. Forsham San Francisco John A. Luetscher, Jr. San Francisco *Bram Rose Montreal Emmerson Ward Rochester	P-7 **Diseases Affecting Absorption from the Gastrointestinal Tract** Moderator *Chester M. Jones Boston Michael J. Lepore New York *Dwight L. Wilbur San Francisco Eric Wollaeger Rochester	P-8 **Roentgenologic Aspects of Heart Disease** Moderator *Howard P. Lewis Portland Charles T. Dotter Portland L. Henry Garland San Francisco *Robert L. King Seattle	P-9 **Animal Diseases Communicable to Man** Moderator *William W. Frye New Orleans James N. DeLamater Pasadena *Rudolph H. Kampmeier Nashville James H. Steele Atlanta Ross B. Denlinger Long Beach	

*F.A.C.P.

PANEL DISCUSSIONS
UNIVERSITY OF SOUTHERN CALIFORNIA CAMPUS

	Bovard Auditorium (Admission by badge; no tickets)	Founders Hall Conference Room A (Admission by ticket only)	Founders Hall Conference Room B (Admission by ticket only)	Founders Hall Conference Room C (Admission by ticket only)	Founders Hall Conference Room D (Admission by ticket only)
Capacity	1500	350	350	170	170
Thursday April 19 11:50 A.M. to 1:10 P.M.	P-10 **Electrocardiograph Conference** Moderator *Frederick Kellogg Long Beach *Joseph M. Barker Beverly Hills *George E. Burch, Jr. New Orleans *Arthur M. Master New York	P-11 **Changing Aspects in the Management of Tuberculosis** Moderator *H. Corwin Hinshaw, Sr. San Francisco *Daniel E. Jenkins Houston *Roger S. Mitchell, Jr. Denver *H. McLeod Riggins New York	P-12 **Sequels of Atherosclerosis** Moderator David Rytand San Francisco *William Likoff Philadelphia *Johannes M. Nielsen Los Angeles Hans H. Zinsser Pasadena	P-13 **The Modern Treatment of Subacute Bacterial Endocarditis** Moderator *Lowell A. Rantz San Francisco *Joseph E. Geraci Rochester William L. Hewitt Los Angeles Ernest Jawetz San Francisco David E. Rogers New York	
Friday April 20 11:50 A.M. to 1:10 P.M.	P-14 **Adding Life to Years** Moderator Robert R. Commons Beverly Hills James A. Hamilton San Francisco Edward E. Henderson Montclair William B. Kountz St. Louis Jessie Marmorston Beverly Hills	P-15 **Neurological Diagnosis Worth Making** Moderator Augustus S. Rose Los Angeles Nicholas A. Bercel Beverly Hills Cyril B. Courville Los Angeles *Karl O. Von Hagen Los Angeles	P-16 **Hemolytic Anemias** Moderator *John S. Lawrence Los Angeles Robert S. Evans Seattle James V. Neel Ann Arbor *Joseph F. Ross Los Angeles *Lawrence E. Young Rochester		

* F.A.C.P.

Panel P-1

Tuesday, April 17

Bovard Auditorium

Aneurysms of the Aorta and Segmental Occlusion of the Aorta, Iliac Arteries and Femoral Arteries

*Edgar V. Allen, Michael E. DeBakey, Charles T. Dotter, Davitt A. Felder, Irving S. Wright

Aneurysms of the abdominal aorta are serious threats to life; they can be removed and replaced with homograft or other prostheses with a mortality rate which is not excessive considering the serious nature of aneurysms of the abdominal aorta. Segmental occlusions of the abdominal aorta, iliac and femoral arteries produce intermittent claudication which is occasionally quite disabling; in appropriate instances these areas of segmental occlusion may be removed and replaced with homograft or other prostheses. The clinical and arteriographic manifestations of these lesions and surgical treatment will be discussed.

Panel P-2

Tuesday, April 17

Founders Hall, Room A

Infections of the Gastrointestinal Tract

*William A. Sodeman, Hamilton H. Anderson, H. W. Brown, Rodney C. Jung

The discussions will include the diagnosis and therapy of cosmopolitan helminthic and protozoal infections common in the United States. The problems of amebiasis, pinworm, and ascaris infection will be included. The acute diarrheal syndromes, as well as the unclassified diarrheas, now on the increase in the United States, will be considered. Diagnostic procedures of especial importance in practice, the best methods of obtaining and preserving specimens for diagnostic study, and the interpretation of the findings will be brought out.

Panel P-3

Tuesday, April 17

Founders Hall, Room B

Clinical Endocrinology for the Internist

*Roberto F. Escamilla, Hans Lisser, E. Perry McCullagh, Paul Starr, Donald R. Wilson

This panel, which is made up of individuals with special interest in clinical endocrinology, will attempt to answer questions submitted by the membership of the College on this subject.

Particular emphasis will be placed on practical applications of the present knowledge of endocrinology in the handling of patients with actual or suspected endocrine diseases, rather than on matters related to the basic sciences.

It is the aim of the panel to keep the discussion as practical and helpful as possible.

Panel P-4

Tuesday, April 17

Founders Hall, Room C

Newer Aspects in the Management of Rheumatoid Arthritis

*William D. Robinson, Edward W. Boland, Ephraim P. Engleman, Charley J. Smyth

This panel will be primarily concerned with an evaluation of the limitations and usefulness of the newer agents which have been introduced for the management of rheumatoid arthritis. At the same time, it will emphasize those methods of therapy which have stood the test of time,

* Moderator.

with particular attention to those modifications of management which are permitted with the use of the newer agents. Specific agents which will be discussed will include: the use of phenylbutazone, the intra-articular use of hydrocortisone and its derivatives, and the systemic use of cortisone and hydrocortisone and their analogues, prednisone and prednisolone.

Panel P-5

Tuesday, April 17

Founders Hall, Room D

Hypersensitivity Mechanisms

*Robert H. Ebert, Robert Good, Sidney Raffel

The panel will deal with some of the recent work on tuberculin hypersensitivity, particularly with regard to passive transfer and compare this with the anaphylactic type of hypersensitivity. Recent advances in the field of allergy will also be considered.

Panel P-6

Wednesday, April 18

Bovard Auditorium

Recent Advances in the Field of Corticoids and Their Application to Therapy

*Peter H. Forsham, John A. Luetscher, Jr., Bram Rose, Emmerson Ward

Recent advances in the understanding of the pathophysiological involvement of the adrenal cortex in edematous, allergic, rheumatoid, and androgenic states will be presented. Following this the differences in potency and side effects, among the latest hydrocortisone derivatives, such as fluorohydrocortisone and prednisolone will be covered, and any clinical advantages in their use in specific disease states will be stressed. Recent experiences in the use of corticoids in the management of the following diseases will be presented for discussion by especially qualified panel members: renal disease, bronchial asthma, allergic dermatitis, collagen diseases in general, endocrinopathies involving the adrenal cortex, and major surgery.

Panel P-7

Wednesday, April 18

Founders Hall, Room A

Diseases Affecting Absorption from the Gastrointestinal Tract

*Chester M. Jones, Michael J. Lepore, Dwight L. Wilbur, Eric Wollaeger

Recent laboratory work is of extreme interest in delineating some of the absorptive functions of the Gastrointestinal Tract. The panel intends to outline some of this recent work and to point out its clinical significance. The emphasis will be on how various disease processes interfere with these normal absorptive functions.

Panel P-8

Wednesday, April 18

Founders Hall, Room B

Roentgenologic Aspects of Heart Disease

*Howard P. Lewis, Charles T. Dotter, L. Henry Garland, Robert L. King

Roentgenologic techniques for the study of the heart and circulation have undergone enormous improvement in recent years. Presently available methods for the study of the heart and circula-

* Moderator.

tion will be discussed from the standpoint of their usefulness and technical difficulty. New techniques, as well as those not now available but in the process of development, will be particularly emphasized. The role of fluoroscopy will be considered. Numerous radiographs will be used to illustrate the discussion.

Panel P-9

Wednesday, April 18

Founders Hall, Room C

Animal Diseases Communicable to Man

*William W. Frye, James N. DeLamater, Rudolph H. Kampmeier, James H. Steele, Ross B. Denlinger

The panel will discuss some diseases of animals which are transmissible to man, particularly Brucellosis, Q-fever, Ornithosis, and the Salmonelloses. Emphasis will be placed on recent developments in epidemiology, diagnosis and treatment.

Panel P-10

Thursday, April 19

Bovard Auditorium

Electrocardiograph Conference

*Frederick Kellogg, Joseph M. Barker, George E. Burch, Arthur M. Master

The Electrocardiographic-Clinical-Pathological Panel will present electrocardiograms illustrating certain points. These will be provided to the participants of the panel prior to its meeting. Copies of these tracings will be found in the program immediately following the CPCs. After discussion of the tracing by a member of the panel, slides with further clinical information will be shown and the panel given a second opportunity to make a diagnosis. Finally the correct diagnosis will be given, illustrated by appropriate slides.

Panel P-11

Thursday, April 19

Founders Hall, Room A

Changing Aspects in the Management of Tuberculosis

*H. Corwin Hinshaw, Sr., Daniel E. Jenkins, Roger S. Mitchell, Jr., H. McLeod Riggins

Treatment of tuberculosis in all of its many forms continues to undergo constant revision. Members of the panel have been selected in part because of their divergent views in such matters as: (1) the need for prolonged bed rest, (2) the place of collapse therapy, (3) the duration and intensity of specific antibacterial drug therapy, (4) the role of pulmonary resection, and (5) the possibility of medical and surgical "cure" of some tuberculous lesions. Recent information concerning such antituberculosis drugs as cycloserine and pyrazinamide will be discussed. Treatment of inactive tuberculosis and management of patients with a recently acquired positive tuberculin test will be discussed.

* Moderator.

Panel P-12

Thursday, April 19

Founders Hall, Room B

Sequels of Atherosclerosis

*David Rytand, William Likoff, Johannes M. Nielsen, Hans H. Zinsser

Much attention has been paid in the past to the late effects of atherosclerosis when this involves the coronary arteries or the branches of the lower aorta, relatively little to similar changes when these occur in the kidneys, other intra-abdominal organs, or even in the central nervous system. Discussion will be directed toward the clinical diagnosis of atherosclerosis of vessels in these regions and toward an evaluation of various methods of treatment.

Panel P-13

Thursday, April 19

Founders Hall, Room C

The Modern Treatment of Subacute Bacterial Endocarditis

*Lowell A. Rantz, Joseph E. Geraci, William L. Hewitt, Ernest Jawetz, David E. Rogers

Early recognition of bacterial endocarditis is of the greatest importance. This will be considered in the light of proper procedure for typical and atypical cases. Modern treatment of disease caused by various organisms will be discussed in detail with special reference to the role of the laboratory and of the use of antibiotics.

Panel P-14

Friday, April 20

Bovard Auditorium

Adding Life to Years

*Robert R. Commons, James A. Hamilton, Edward E. Henderson, William B. Kountz, Jessie Marmorston

Prevention and treatment of endocrine, nutritional and psychological morbidity in older persons. Does an endocrine cocktail add spice to life, i.e., "life to years"?

Panel P-15

Friday, April 20

Founders Hall, Room A

Neurological Diagnosis Worth Making

*Augustus S. Rose, Nicholas A. Bercel, Cyril B. Courville, Karl O. Von Hagen

The nature, differential diagnosis, and practical management of several common disorders of the nervous system including epilepsy, strokes and neuritis will be discussed.

* Moderator.

Panel P-16

Friday, April 20

Founders Hall, Room B

Hemolytic Anemias

† JOHN S. LAWRENCE, ROBERT S. EVANS, JAMES V. NEEL, JOSEPH F. ROSS, LAWRENCE E. YOUNG

Basic abnormalities in some of the hemolytic anemias will be open for discussion. The importance of genetic patterns in reference to abnormal hemoglobins, the abnormal metabolic patterns in erythrocytes of congenital hemolytic jaundice, the differentiation of acquired hemolytic anemia from hereditary spherocytosis with emphasis on the underlying abnormalities and their treatment, and finally, the place of radioactive substances in the study of these disorders represent some of the subjects which the members of the panel are well qualified to discuss.

Academic Index

Panel Participants

E. V. ALLEN, M.D., F.A.C.P.
Senior Consultant, Mayo Clinic; Professor of Medicine, University of Minnesota, Mayo Foundation.

*HAMILTON H. ANDERSON, M.D.
Professor of Pharmacology and Experimental Therapeutics, University of California School of Medicine.

*JOSEPH M. BARKER, M.D., F.A.C.P.
Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

*NICHOLAS A. BERCEL, M.D.
Past President, Western Society of Electro-encephalography; Visiting Associate Professor of Physiology, University of Southern California School of Medicine.

EDWARD W. BOLAND, M.D., F.A.C.P.
1954 President, American Rheumatism Association.

*H. W. BROWN, M.D.
Director, School of Public Health and Administrative Medicine, Columbia University College of Physicians and Surgeons; Consultant in Parasitology, Presbyterian Hospital in the City of New York.

GEORGE E. BURCH, M.D., F.A.C.P.
Henderson Professor and Chairman, Department of Medicine, Tulane University of Louisiana School of Medicine; Member, National Advisory Heart Council; Editorial Board, American Journal of Medical Sciences.

ROBERT R. COMMONS, M.D., (Associate)
Assistant Clinical Professor of Medicine, University of Southern California School of Medicine; Senior Attending Staff and Chief of Endocrine Clinic, Los Angeles County General Hospital; Director, Gerontological Unit, Good Hope Medical Foundation.

*CYRIL B. COURVILLE, M.D.
Consultant, Coroner's Office, Los Angeles County; Professor of Nervous Diseases, College of Medical Evangelists.

*MICHAEL E. DEBAKEY, M.D.
Judson L. Taylor Professor of Surgery, Chairman of the Department of Surgery, Baylor University College of Medicine.

† Moderator.
* By invitation.

JAMES N. DELAMATER, M.D., (Associate)
Clinical Professor of Medicine, University of Southern California School of Medicine; Epidemiologist, Los Angeles County Medical Research Foundation.

*ROSS B. DENLINGER, M.D.
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*CHARLES T. DOTTER, M.D.
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ROBERT H. EBERT, M.D., F.A.C.P.
Markle Scholar from '48; Consultant, Chicago State Tuberculosis Sanitarium; Professor of Medicine, University of Chicago, The School of Medicine.

EPHRAIM P. ENGLEMAN, M.D., F.A.C.P.
Chief of the Rheumatic Fever Center at Torney General Hospital, Palm Springs (Calif.); Assistant Clinical Professor of Medicine, University of California School of Medicine.

ROBERTO F. ESCAMILLA, M.D., F.A.C.P.
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*ROBERT S. EVANS, M.D.
Associate Professor of Medicine, University of Washington School of Medicine; Chief of Medicine, Veterans Administration Hospital, Seattle.

*DAVITT A. FELDER, M.D.
Assistant Professor in Surgery, University of Minnesota Medical School; Head, Peripheral Vascular Clinic, University of Minnesota Hospitals.

*PETER H. FORSHAM, M.D.
Research Fellow in Medicine, '44–'45 and '46–'48 (both at Harvard); Associate Professor of Medicine and Pediatrics, University of California School of Medicine.

WILLIAM W. FRYE, M.D., F.A.C.P.
Professor of Tropical Medicine and Dean, Louisiana State University School of Medicine; Member, Commission on Enteric Infections (Armed Forces Epidemiological Board).

*L. HENRY GARLAND, M.D.
Clinical Professor of Radiology, Stanford University Medical School; Chairman, Committee on Cancer Diagnosis and Therapy, National Research Council; Past President, Radiological Society of North America and American College of Radiology.

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*EDWARD E. HENDERSON, M.D.
Trustee, American Geriatric Research Society (President '53); President, American Geriatrics Society; Editor-in-Chief of Geriatrics.

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* By invitation.

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Frederick Kellogg, M.D., F.A.C.P.
Clinical Instructor of Medicine, University of Southern California School of Medicine; President, California Heart Association, 1955–56.

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* By invitation.

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Paul Starr, M.D., F.A.C.P.
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*James H. Steele, D.V.M.
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* By invitation.

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THE CLINIC SESSIONS

Color Television of Hospital Clinics

As an innovation, all hospital clinics will be televised from the Los Angeles County General Hospital directly to the Lower Level of the Shrine Auditorium, Exposition Hall. This makes it unnecessary for the visiting physicians to travel long distances to the wide-spread hospitals participating in the program. Another new feature will be two-way radio communication between the telecasting room at the Los Angeles County General Hospital and the receiving room at the Shrine Auditorium. All Moderators will be in front of the audience at the Shrine Auditorium.

Various hospitals and institutions and their respective staffs are co-operating. Due to changing programs from one group to another, a slight lag will occur. However, it is believed that the times indicated will be approximately correct. This program is made possible through the co-operation of the Smith, Kline and French Laboratories, of Philadelphia, Columbia Broadcasting Company, Paramount Studios, and the Los Angeles County General Hospital. Large screens will be provided instead of the multiple, small screens formerly used. The clinics are deemed to be of such value that they will be kinescoped for future teaching purposes.

Admission by regular badge; no special tickets required.

* By invitation.

Tuesday, April 17, 1956

Moderator: Donald C. Balfour, Jr.

A.M.

9:00– 9:30 Separation of the Formed Elements of the Blood and Fluids, and Their Clinical Use.

HOWARD R. BIERMAN, KEITH H. KELLY
City of Hope Medical Center, Duarte.

Leukocytes, platelets and erythrocytes can now be separated from plasma by the ADL—Cohn Blood Fractionator for clinical employment. The benefits of these fractions in specific illnesses, and the preparation of cellular sediments from urine, pleural and peritoneal effusions will be exhibited. The clinical applications of these fractions will be shown.

9:30–10:30 Portal Hypertension.

TELFER B. REYNOLDS, WILLIAM P. MIKKELSEN, ARTHUR C. PATTISON, ALLAN G. REDEKER, HERMAN W. GELLER
Los Angeles County General Hospital.

This presentation deals with the medical and surgical aspects of portal hypertension. To be illustrated are: the etiology of portal hypertension; assessment of its severity of hepatic vein catheterization; emergency therapy of bleeding esophageal varices, and surgical decompression of the portal bed.

10:30–11:00 Studies of Urinary Porphyrin Excretion in Certain Pathological Conditions.

REX STERLING, ALLAN G. REDEKER, MARION MCMAHON
Los Angeles County General Hospital.

A close correlation by the efforts of the clinician and the biochemist has led to a better understanding of conditions associated with abnormal porphyrin excretion. Some interesting urinary porphyrin excretion patterns and their clinical implications will be presented.

11:00–11:30 INTERMISSION.

Tuesday, April 17, 1956

Moderator: Thomas H. Brem

A.M.

11:30–12:00 Cine Roentgenography of Diaphragmatic Motion.

GEORGE M. CAMPION, IRVING REHMAN, RICHARD E. OTTOMAN
St. Joseph Hospital, Burbank, and Walt Disney Research Foundation, Los Angeles.

A discussion of the changes in outline, motility, and position of the diaphragm in different pathological states, intrinsic to the diaphragm, and in certain diseases of the lungs will be presented with special motion picture filming of fluoroscopic observations.

P.M.

12:00–12:30 Diagnosis and Treatment of Pulmonary Ventilatory Failure.

JOHN E. AFFELDT, MILTON G. CRANE, JACK D. HACKNEY, STANLEY N. ROKAW
Rancho Los Amigos Hospital, Respiratory Center for Poliomyelitis, Hondo.

The Infra-red CO_2 Analyser is used to diagnose pulmonary ventilatory failure by measuring alveolar or mixed venous CO_2 levels. The tank respirator and/or tracheotomy are useful in treating terminal failure in asthma, emphysema, thoracic fixation and poliomyelitis. Such cases with laboratory studies will be presented.

12:30– 1:00 **The Recognition and Management of Respiratory Acidosis.**

REGINALD H. SMART, HURLEY L. MOTLEY, JOSEPH F. BOYLE
Hospital of the Good Samaritan, Los Angeles.

Patients die daily of unrecognized respiratory acidosis although certain clinical manifestations should arouse the physician's suspicion. There are simple diagnostic laboratory procedures that ought to be available in every hospital. These will be presented with demonstrations of arterial blood pH determinations, effective methods of treatment, and illustrative cases.

Wednesday, April 18, 1956

Moderator: John S. Lawrence

A.M.

9:00–10:00 **A Hematology Clinic.**

SAMUEL I. RAPAPORT, EMMETT B. REILLY, FRANK W. ELLIS, BERNARD WINTER, GURTH CARPENTER, WILLIAM N. VALENTINE, EDMUND L. DUBOIS
Veterans Administration Hospital, Long Beach, and Los Angeles County General Hospital.

Patients with hematologic disorders will be presented along with colored microphotographs of their altered blood and bone marrow findings. There will be examples of sickle-cell thalassemia, myelofibrosis with extramedullary hematopoiesis, Hodgkin's disease of bone, hemochromatosis treated by venesections, hypersplenism complicating lymphosarcoma and systemic lupus erythematosus.

10:00–10:30 **Coccidioidomycosis.**

ROGER O. EGEBERG, ANN F. ELCONIN, ROBERT WIER, ROBERT LUBARSKI
Veterans Administration Center, Los Angeles.

With the aid of colored movies, x-ray films, diagrams, maps, and laboratory equipment, a little of the story of coccidioidomycosis will be told. This will cover a brief discussion on the probable source of infection (the soil), the area of distribution, the clinical picture, and the laboratory aspects of primary disease and its complications; and the clinical picture and the laboratory aspects of the disseminated disease, the basis for diagnosis, determination of prognosis, and a brief review of the treatment.

10:30–11:00 **Renal Tubular Acidosis.**

TELFER B. REYNOLDS, HELEN E. MARTIN
Los Angeles County General Hospital.

The clinical and biochemical abnormalities of renal tubular acidosis will be summarized by presentation of three patients, with illustrative charts and x-rays. Results of investigative studies of intravenous loading with neutral isotonic phosphate and bicarbonate, and oral loading with both a weak and strong acid in these patients will be shown, and discussed with reference to the pathogenesis of the biochemical defect.

11:00–11:30 INTERMISSION.

Moderator: Paul Starr

11:30–12:00 **Camp Training for Young Diabetics.**

WILLIAM H. GRISHAW, JOHN M. MASSON
Hospital of the Good Samaritan, Los Angeles.

"Camp for Diabetic Children" titles a 20-minute narrated motion picture on Uni-Betic Camp in the San Bernardino mountains of California. The camp is sponsored by the non-profit Los Angeles Metabolic Clinic. The film is primarily designed to show that these children, 8 through 16 years, can lead normal lives and enjoy normal camp activity despite their diabetes.

P.M.

12:00–12:20 Hypoadrenalism: A Routine Therapy and Clinical Presentation.

STANFORD A. FURER, ROBERT P. NATELSON
Los Angeles County General Hospital.

This clinical review of ambulatory care of Addison's disease reveals the striking success of oral substitute steroid therapy in returning these patients to a normal life. Patients presented have been successfully maintained for one or more years without complications on oral hydrocortisone, methyltestosterone, added salt, and, in some cases, small doses of desoxycorticosterone acetate.

12:20–12:40 Hypophysectomy in the Treatment of Mammary Carcinomatosis.

ARTHUR C. PATTISON, H. RUSSELL FISHER, DONALD W. PETIT, DONALD B. FRESHWATER
Huntington Memorial Hospital, Pasadena.

Our experience with total hypophysectomy for mammary carcinomatosis has helped to confirm earlier encouraging reports. A newer technique of rapid, safe hypophysectomy virtually guarantees total removal, a sine qua non of effectiveness. All physicians should understand patient selection in a general way and consider hypophysectomy in hormonally fed mammary carcinomatosis as early as possible.

12:40– 1:00 Newer Application of Paper Electrophoresis to the Problems of Clinical Medicine.

REUBEN STRAUS, MOSES WURM, BRUCE D. HARROLD
St. Joseph Hospital, Burbank.

Experience with the quantitation of serum proteins separated by paper electrophoresis is proving this procedure to be a reliable diagnostic adjunct. The method of preparing protein patterns on paper will be demonstrated by motion pictures and selected abnormal curves will be discussed qualitatively and quantitatively in relation to a variety of clinical diagnoses. These observations will be compared and correlated with published data secured by moving boundary electrophoresis.

Thursday, April 19, 1956

Co-Moderators: George C. Griffith, Richard S. Cosby

A.M.

9:00– 9:30 Intramural Electrocardiography.

MYRON PRINZMETAL, ALFRED GOLDMAN, RASHID MASSUMI, LOIS SCHWARTZ, REXFORD KENNAMER, HUBERT PIPBERGER, LOUIS RAKITA, JEAN-LOUIS BORDUAS
Cedars of Lebanon Hospital, Los Angeles, and City of Hope Medical Center, Duarte.

This demonstration is concerned with the genesis of the electrocardiographic deflection in man and dog. Investigations were made on normal hearts and hearts with coronary artery disease. The manner in which the ECG components develop and the contribution made by the various myocardial layers is shown.

9:30–10:00 The Serum Transaminase Test in Myocardial Infarction.

ALBERT A. KATTUS, JR., ROBERT WATANABE, CLARENCE M. AGRESS
Veterans Administration Center, Los Angeles.

One or more serum transaminase determinations have been made on a series of 430 patients. A discussion of procedure and results will be given showing the clinical and laboratory use of this test and its significance.

10:00–10:15 **A Clinical Laboratory Profile for Atherosclerosis.**
WILLARD J. ZINN
Los Angeles County General Hospital.

The association of poor serum lipid emulsification, clinical atherosclerosis, and diseases with reversed A/G ratios will be demonstrated by illustrations. Methods used for the investigation of atherosclerosis will be shown in action at the laboratory.

10:15–10:30 **Hypertension Due to Cirsoid Aneurysm of the Renal Artery.**
THOMAS H. BREM, HERBERT J. MOVIUS, EUGENE TEMKIN
Veterans Administration Hospital, Long Beach.

Two case reports of patients in their early twenties with known hypertension of five and seven years' duration will be presented. Aortography in both instances disclosed vascular plexuses arising from the renal arteries. The anomaly is probably an arterial venous cirsoid aneurysm of the renal arteries, an entity not previously described, and the studies and surgery in one case will be discussed.

10:30–11:00 **Heart Block with Slow Ventricular Rate: Hemodynamic Ballistocardiographic and Vectorcardiographic Studies.**
DAVID C. LEVINSON, JOHN P. MEEHAN, JR., LEWIS GUNTHER, STEPHEN R. ELEK, MORRIS WILBURNE, JULIEN H. ISAACS, RAYMON J. SPRITZLER
Cedars of Lebanon Hospital, Los Angeles.

Five patients with chronic heart block and slow ventricular rates (less than 40 per minute) have been studied. The findings at cardiac catheterization will be correlated with ballistocardiographic and vectorcardiographic studies.

11:00–11:30 INTERMISSION.

Moderator: Clarence J. Berne

11:30–12:00 **Total Adrenalectomy in the Management of Severe Hypertension.**
EUGENE J. ELLIS, EDWARD B. MERCHANT, JOHN L. REYNOLDS
St. Vincent's Hospital, Los Angeles.

Total adrenalectomy may be an elective means of controlling severe hypertension that has failed to respond to medical treatment. Certain fundamental mechanisms in hypertension have been suggested by responses noted to hypotensive agents, sodium, and the various adrenal steroids used in the management of patients adrenalectomized for this condition.

P.M.

12:00–12:30 **Aneurysms of the Abdominal Aorta.**
J. HOWARD PAYNE, TRAVIS WINSOR, LELAND HAWKINS, HERBERT J. MOVIUS, WALTER P. MARTIN, MAX R. GASPAR
Los Angeles County General Hospital, Hospital of the Good Samaritan, Los Angeles, Veterans Administration Hospital, Long Beach, Harriman Jones Clinic and Hospital, Long Beach.

The problems presented to the physician by a patient with an aneurysm of the abdominal aorta will be illustrated. The prognosis, methods of evaluation and selection of those patients suitable for surgical therapy will be emphasized. Important aspects of the surgical excision and replacement with a "graft" will be demonstrated.

12:30– 1:00 **Diagnosis and Treatment of Pheochromocytoma.**
JOHN MARTIN ASKEY, A. C. P. BAKOS, ROBERT C. SURRIDGE
St. Vincent's Hospital, Los Angeles.

A panel discussion supplemented by a 20-minute titled film, depicting diagnostic procedures and the surgical treatment of pheochromocytoma. The importance of suspecting the presence of pheochromocytoma in all patients with a hypertensive syndrome is stressed. The film illustrates and documents the exact preoperative and operative medical management in this disease.

Friday, April 20, 1956

Moderator: John E. Peterson

A.M.

9:00– 9:30 Sudden Unexpected Death on Functional Basis: A Chapter of Psychosomatic Medicine.

JULIUS BAUER, IRVING GORDON, HARRY ROTH
Los Angeles County General Hospital.

Sudden unexpected death on functional basis attracted a great deal of attention, particularly from the viewpoint of legal medicine, in the first three decades of this century. Hyperplasia of the thymus and lymphatic tissue, hypoplasia of the aorta and chromaffine tissue have been found at autopsy of many such cases. Ventricular fibrillation without evident cause except for emotional shock appeared to be the most satisfactory explanation. A case of this type, sudden death during psychiatric interview of a patient with bronchial asthma, is reported.

9:30–10:00 Atrophic Gastritis—Is It a Clinical Entity?

OLOV A. BLOMQUIST, RUDOLF SCHINDLER
White Memorial Hospital, Los Angeles.

Whether or not atrophic gastritis is a clinically important entity is a much debated question. This problem will be discussed by the presentation of patients and by analyses of statistical data. For this analysis patients have been chosen who have atrophic gastritis gastroscopically, but no evidence of any other disease, organic or functional.

10:00–10:30 Studies on the Motility of the Gastrointestinal Tract.

WILLIAM H. BACHRACH
Veterans Administration Center, Los Angeles.

This presentation will consist of a demonstration of the equipment used and the procedure followed in recording motor activity from various parts of the gastrointestinal tract. The type of tracing which can be obtained with this method will be illustrated and certain practical applications of motility studies will be described.

10:30–11:00 Experimental Evaluation of Antral Effect on Peptic Ulceration.

DAVID STATE
Cedars of Lebanon Hospital, Los Angeles.

In a series of dogs we have shown that the antrum, when left in continuity with the acid secreting mucosa, appears to protect the animal from histamine induced ulceration, and that the protective action apparently is a specific function of the antrum. With this experimental background we have utilized segmental gastric resections in 36 patients. The advantages of this operation will be discussed and patients presented, to indicate their response to this operative procedure.

11:00–11:30 INTERMISSION.

Moderator: Augustus S. Rose

11:30–12:00 Demonstration of Neurological Cases.

J. M. NIELSEN, THEODORE KURZE, LAWRENCE JACOBS
Los Angeles County General Hospital.

Cases of various neurological diseases will be presented with succinct statements of the condition and the findings.

P.M.

12:00–12:30 Rehabilitation of the Hemiplegic Patient.

ROBERT V. MILLER, JR., ROBERT L. SMITH
Veterans Administration Center, Los Angeles.

It is estimated that there are approximately 1,250,000 hemiplegic patients in the United States and that they constitute one of the largest groups of

individuals suffering from chronic neurological disease. The purpose of a program of rehabilitation is to retrain the patient to ambulate, perform the necessary acts of daily living and to obtain the maximum use of the individual's physical capabilities so that he may become as independent as possible.

12:30– 1:00 Dermatology Clinic.

MAXIMILIAN E. OBERMAYER, NELSON PAUL ANDERSON, SAMUEL WILLIAM BECKER

Los Angeles County General Hospital, and Veterans Administration Hospital, Long Beach.

a) Neurodermatitis or atopic dermatitis is of considerable economic importance. Its multiple causal, predisposing and precipitating factors have been of baffling interest to physicians of several specialties, chiefly dermatologists, allergists and psychiatrists, as well, of course, as internists. These factors are illustrated by the presentation of patients and/or slides. The therapeutic Do's and Don't's are discussed.

b) This presentation will stress the early recognition of malignant lentigo and melanoma. The clinical signs of malignant change will be illustrated by the presentation of patients, charts and slides. The differential diagnosis from apparently similar but benign conditions will be considered.

c) Eruptions following administration of streptomycin and/or isonicotinic hydrazide often resemble the so-called functional (neurosomatic or psychosomatic) dermatoses. These drugs are known as "neurotoxic," and have produced diseases of the central, sympathetic and peripheral nervous systems. The possible allergic nature of such cutaneous reactions is discussed.

Academic Index

TV Program Participants

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JOHN MARTIN ASKEY, M.D., F.A.C.P.
Associate Clinical Professor of Medicine, University of Southern California School of Medicine.

*WILLIAM H. BACHRACH, M.D., Ph.D.,
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AUGUSTUS C. P. BAKOS, M.D., (Associate)
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DONALD C. BALFOUR, JR., M.D., (Associate)
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JULIUS BAUER, M.D., F.A.C.P.
Clinical Professor of Medicine, College of Medical Evangelists.

*SAMUEL WILLIAM BECKER, M.D.
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* By invitation.

*Clarence J. Berne, M.D.
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*Rashid Massumi, M.D.
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* By invitation.

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*William N. Valentine, M.D.
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* By invitation.

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TV Program

Ted Bloodhart, Chairman

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Eleanor Gerlach
Cedars of Lebanon Hospital.
Ozzie Glover
Free Lance Cinematographer.
Ed Hamilton
College of Medical Evangelists—White Memorial Hospital.
Lucille Innes
College of Medical Evangelists—White Memorial Hospital.
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William Renner
St. Joseph Hospital, Burbank.
Zoltan Yuhasz
St. Vincent's (Los Angeles) and Huntington Memorial (Pasadena) Hospitals.

Financial assistance from The William S. Merrell Company for art work is gratefully acknowledged.

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SCIENTIFIC EXHIBITS

This is a new undertaking for the College. The Board of Regents has permitted the Western Medical Schools to exhibit their scientific material. The purpose of these exhibits is to provide opportunity for the faculty members of Western Schools to become better acquainted with the work of their colleagues and with the membership of the College. Additionally, the College has accepted exhibits by the U. S. Air Force, Armed Forces Institute of Pathology, the Muscular Dystrophy Associations of America, the National Foundation for Infantile Paralysis, and the recently organized Commission on Professional and Hospital Activities in conjunction with the American College of Surgeons (Medical Audit). You are urged to visit the scientific exhibits which are located on the balcony of the Shrine Exposition Hall.

Space 1

Adrenal Steroid Estimation in Blood
University of British Columbia School of Medicine

MARVIN DARRACH, M.,D., and H. W. MCINTOSH, M.D.

Space 2

The Antacid Effect of Dihydroxyl Aluminum Aminoacetate and Its Use in the Treatment of Peptic Ulcer
University of California School of Medicine, San Francisco

J. ALFRED RIDER, M.D., Ph.D., JOHN O. GIBBS, M.D., (Associate), JOYCE SWADER, B.S., and T. L. ALTHAUSEN, SR., M.D., F.A.C.P.

Space 3

Lymph Node Imprints
University of Oregon Medical School

R. D. KOLER, M.D., NELSON NILES, M.D., A. J. SEAMAN, M.D., (Associate), and EDWIN E. OSGOOD, M.D., F.A.C.P.

Space 4

Lung Biopsy in Diffuse Pulmonary Diseases
University of Oregon Medical School

JOHN E. TUHY, M.D., and GORDON MAURICE, M.D.

Space 5

New Digitalis Glycosides: Acetyl-Digitoxin
University of Oregon Medical School

ISIDOR C. BRILL, M.D., F.A.C.P., PAUL R. BURGNER, M.D., and NORMAN A. DAVID, M.D.

Space 6

Collimators for Gamma Radioscopy
Stanford University School of Medicine

R. R. NEWELL, M.D.

Space 7

Graphic Demonstrations of the Anatomy of the Thorax
Stanford University School of Medicine

DAVID BASSETT, M.D.

Space 8

Cancer Chemotherapy

Stanford University School of Medicine

BYRON E. HALL, M.D., F.A.C.P., FORREST M. WILLETT, M.D., F.A.C.P., and THOMAS FEICHTMEIER, M.D.

Space 9

Cardiac Physiology

Stanford University School of Medicine

FORREST M. WILLETT, M.D., F.A.C.P., and ARTHUR SELZER, M.D., (Associate)

Space 10

Cycloserine in the Treatment of Tuberculosis

Stanford University School of Medicine

H. CORWIN HINSHAW, SR., M.D., F.A.C.P.

Space 11

Treatment of Chronic Congestive Heart Failure with Neohydrin for 8–53 Months

University of Southern California School of Medicine

SIM P. DIMITROFF, M.D., (Associate), and GEORGE C. GRIFFITH, M.D., F.A.C.P.

Space 12

Portal Hypertension

University of Southern California School of Medicine

DONALD C. BALFOUR, JR., M.D., (Associate), HERMAN M. GELLER, M.D., MILTON R. HALES, M.D., WILLIAM P. MIKKELSEN, M.D., ARTHUR C. PATTISON, M.D., and ALLAN G. REDEKER, M.D.

Space 13

Therapy of Thyroid Cancer

University of Southern California School of Medicine

PAUL STARR, M.D., F.A.C.P., DONALD W. PETIT, M.D., BORIS CATZ, M.D., HAROLD SCHWARTZ, M.D., and FREMONT DAVIS, M.D.

Space 14

Collateral Coronary Circulation

University of California School of Medicine, Los Angeles

ELIOT CORDAY, M.D., (Associate), LAURO B. DE VERA, M.D., and HERBERT GOLD, M.D.

Space 15

Porphyria

University of Southern California School of Medicine

REX E. STERLING, Ph.D., ALLAN G. REDEKER, M.D., MARION MCMAHON, and NEIL Y. CHIAMORI

Space 16

Trace Metal Studies in Human Disease with Special Reference to Metal Patterns in Wilson's Disease, Hemochromatosis and Refractory Anemia
University of Southern California School of Medicine

EDWARD M. BUTT, M.D., ROGER MCKENNA, M.D., RALPH NUSBAUM, M.D., and GEORGE C. GRIFFITH, M.D., F.A.C.P.

(With the technical assistance of SAMUEL DIDIO and TOM GILMOUR)

Space 17

Experimental Studies on the Revascularized Dog Kidney
University of Southern California School of Medicine

YALE J. KATZ, M.D.

Space 18

The Graphic Registration of Cardiac Thrills
University of Southern California School of Medicine

DAVID C. LEVINSON, M.D., JOHN P. MEEHAN, M.D., and LEONARD SCHWARTZ, M.D.

Space 19

Clinical Vectorcardiography
University of Southern California School of Medicine

STEPHEN R. ELEK, M.D., F.A.C.P., J. LOUIS FREIBRUN, M.D., and GEORGE C. GRIFFITH, M.D., F.A.C.P.

Space 20

Clinical Experience with Acetyl-Digitoxin
University of Southern California School of Medicine

MARTIN GOLDFARB, M.D., M. C. THORNER, M.D., F.A.C.P., and GEORGE C. GRIFFITH, M.D., F.A.C.P.

Space 21

Renal Stone Registry
University of Southern California School of Medicine

HANS H. ZINSSER, M.D., DONALD A. CHARNOCK, M.D., JAY J. CRANE, M.D., HAROLD FRANKL, M.D., and PLATO GRIVAS

Spaces 22 and 23

Pulmonary Function
College of Medical Evangelists

JOHN E. AFFELDT, M.D., MILTON G. CRANE, M.D., and JACK D. HACKNEY, M.D.

Space 24

Correlation of the Electroencephalogram and pCO_2 Levels
College of Medical Evangelists

LESLIE B. MANN, JR., M.D., (Associate), LEONARD WENDLAND, Ph.D., JOHN E. AFFELDT, M.D., STANLEY N. ROKAW, M.D., and MILTON G. CRANE, M.D.

Space 25

Differential Diagnosis of Diseases of the Stomach

College of Medical Evangelists

RUDOLPH SCHINDLER, M.D., F.A.C.P., and VERNON M. PARRETT, M.D.

Space 26

Experimental Nephrosis

College of Medical Evangelists
(Medical Research Programs, V.A. Administration Hospital, Long Beach)

FRED MODERN, M.D., F.A.F.P., CAROLYN PIEL, M.D., JOSEPH R. GOODMAN, Ph.D., LUTHER DONG, and ROGER MOORE

Space 27

The Cerebral Atrophies of the Adult

College of Medical Evangelists

EDISON D. FISHER, M.D., F.A.C.P.

Space 28

Cardiac Output Measured by the Injection Method Using Radioactive Material and Continuous Recording

College of Medical Evangelists

MILTON G. CRANE, M.D., JOHN E. HOLLOWAY, M.D., RALPH M. ADAMS, B.A., and IVOR C. WOODWARD, M.A.

Space 29

The Anatomical and Topographical Delineation of Angina Pectoris and Heart Pain

College of Medical Evangelists

LEWIS GUNTHER, M.D., F.A.C.P.

Space 30

Medical Aspects of Cholinesterase

College of Medical Evangelists

MELVIN I. HALEY, Ph.D., and DONALD JONES, B.A.

Space 31

Renal Function under Deep Anesthesia

College of Medical Evangelists

VERNON C. BOHR, Ph.D., and RICHARD S. RALLS, M.S.

Space 32

The Artificial Heart-Lung Machine and Its Possible Uses in Internal Medicine

Institute for Medical Research
Cedars of Lebanon Hospital

PETER F. SALISBURY, M.D., Ph.D.

Space 33

The Mechanism of Experimental Coronary Shock
University of California School of Medicine, Los Angeles

CLARENCE M. AGRESS, M.D., F.A.C.P., HOWARD I. JACOBS, M.S., HARVEY F. GLASSNER, A.B., and MAXWELL J. BINDER, M.D., (Associate)

Space 34

The Effects of Irradiation on the Eye
University of California School of Medicine, Los Angeles

ROBERT M. SINSKEY, M.D.

Space 35

The Pathologic Changes in Pulmonary Hemosiderosis
University of California School of Medicine, Los Angeles

ROY WALFORD, M.D., and LEO KAPLAN, M.D.

Space 36

Percutaneous Antegrade Pyelography and Hydronephrosis
University of California School of Medicine, Los Angeles

WILLIAM C. CASEY, M.D., and WILLARD E. GOODWIN, M.D.

Space 37

The Selection of Candidates
for the Direct Surgical Treatment of Arteriosclerosis
University of California School of Medicine, Los Angeles

WILEY F. BARKER, M.D., and JACK A. CANNON, M.D.

Space 38

Demonstration of Surface Lesions by a Wax Replica Technique
University of California School of Medicine, Los Angeles

HANS GEBHARDI, M.D.

Space 39

Iron Metabolism and Hemochromatosis
University of California School of Medicine, Los Angeles

WILLIAM FIGUEROA, M.D., and LEON ROSOVE, M.D., F.A.C.P.

Space 40

Leukopheresis
University of California School of Medicine, Los Angeles

CHARLES G. CRADDOCK, JR., M.D., (Associate)

Space 41

Serum Transaminase Level as an Aid in the Diagnosis and Prognosis of Acute Myocardial Infarction
University of California School of Medicine, Los Angeles

ALBERT A. KATTUS, JR., M.D., and ROBERT WATANABE, M.D.

Space 42

Abdominal Venography
University of California School of Medicine, Los Angeles
JOSEPH J. KAUFMAN, M.D., JOHN WATKINS, M.D., DONALD E. BURKE, M.D., and WILLARD E. GOODWIN, M.D.

Space 43

Histopathogenetic Basis of Dissecting Aortic Aneurysms
University of Oregon Medical School
(and Research Laboratory of Medical Service, V.A. Hospital, Portland)
DONALD G. WALKER, Ph.D., and ZOLTON T. WIRTSCHAFTER, M.D., F.A.C.P.

Space 44

Rose Bengal Liver and Differential Kidney Function
University of California School of Medicine, Los Angeles
GEORGE V. TAPLIN, M.D., and LESLIE R. BENNETT, M.D.

Space 45

Thyroid Scanning
University of California School of Medicine, Los Angeles
LESLIE R. BENNETT, M.D., and JOSEPH WESTOVER, M.D.

Space 46

The Management of Gastric Ulcer
University of California School of Medicine, Los Angeles
WILLIAM H. BACHRACH, M.D.

Space 47

Non-thyroid Uses for Isotopes in Diagnosis
University of California School of Medicine, Los Angeles
FRANZ K. BAUER, M.D., (Associate)

Space 48

The Evolution of Renal Function Reserve by Clinical Tests
University of California School of Medicine, Los Angeles
RALPH GOLDMAN, M.D., F.A.C.P.

Space 49

The Treatment of Epilepsy in Veterans Domiciled at the Veterans Administration Center, Los Angeles
University of California School of Medicine, Los Angeles
HARRY FANG, M.D.

Space 50

Superior Vena Cava Syndrome
U.S. Air Force, Armed Forces Institute of Pathology

Space 51

Manifestations of Muscular Dystrophy
Muscular Dystrophy Associations of America

Space 52

Medical Audit
Commission on Professional and Hospital Activities
and
The American College of Surgeons

VERGIL N. SLEE, M.D., (Associate), Director of the Commission
C. WESLEY EISELE, M.D., F.A.C.P., ACP Trustee of the Commission
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This exhibit will show a new, practicable and effective method by which the medical staff can conduct its own medical audit of the work done by all branches of medicine. The method is based on the premise that adequate hospital statistics will indicate the areas of medical practice most in need of scrutiny by the medical staff. Modern business machines are used in the statistical analysis of medical practice and for the preparation of disease, operation, and physician indexes for the medical records department. Forms which simplify the analysis by the medical staff of the quality of patient care will be shown.

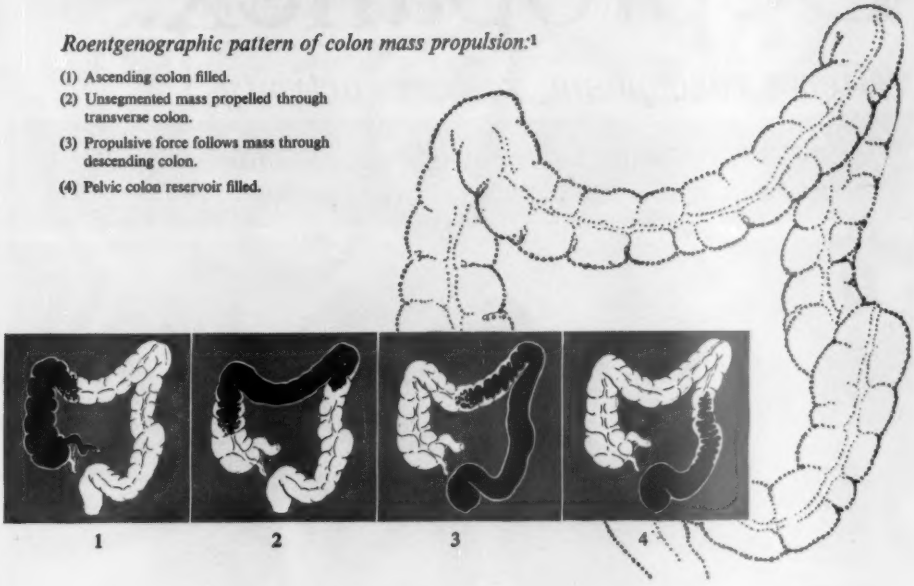
Space 53

Rehabilitation of Poliomyelitis Patients with Respiratory Involvement
National Foundation for Infantile Paralysis

SMOOTHAGE ACTION IN CONSTIPATION

Roentgenographic pattern of colon mass propulsion:[1]

(1) Ascending colon filled.
(2) Unsegmented mass propelled through transverse colon.
(3) Propulsive force follows mass through descending colon.
(4) Pelvic colon reservoir filled.



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1. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice: A Text in Applied Physiology, ed. 5, Baltimore, The Williams & Wilkins Company, 1950, pp. 579-583.
2. Bargen, J. A.: A Method of Improving Function of the Bowel, Gastroenterology *13*:275 (Oct.) 1949.

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REFERENCES: 1. Am. Heart J. 18:425, 1939. 2. J. Urol. 51:137, 1944. 3. Minnesota Med. 33:103, 1950.

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1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct., 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

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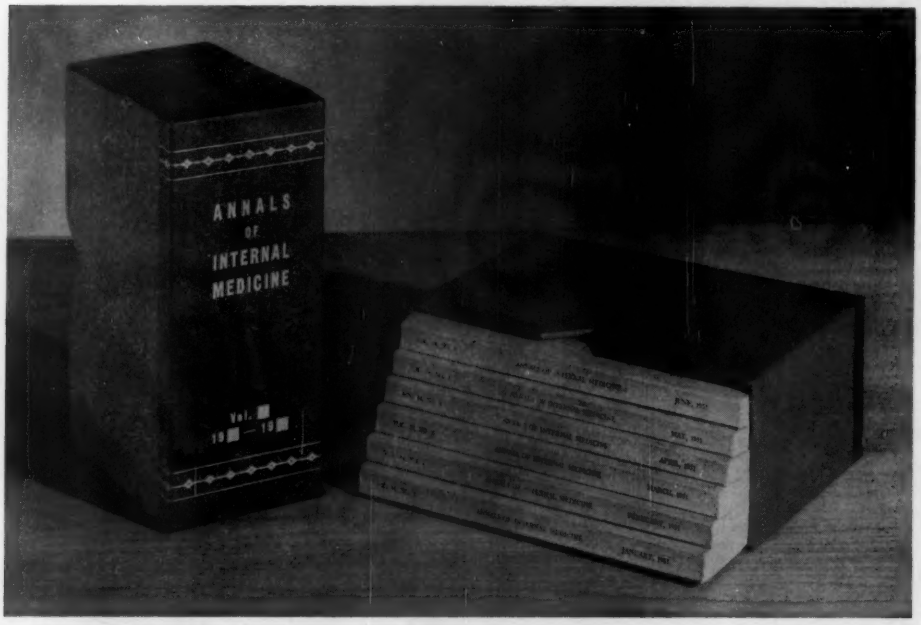

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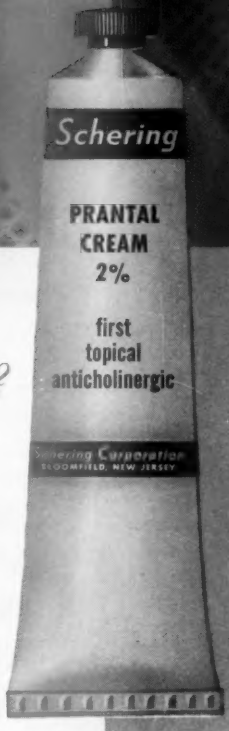

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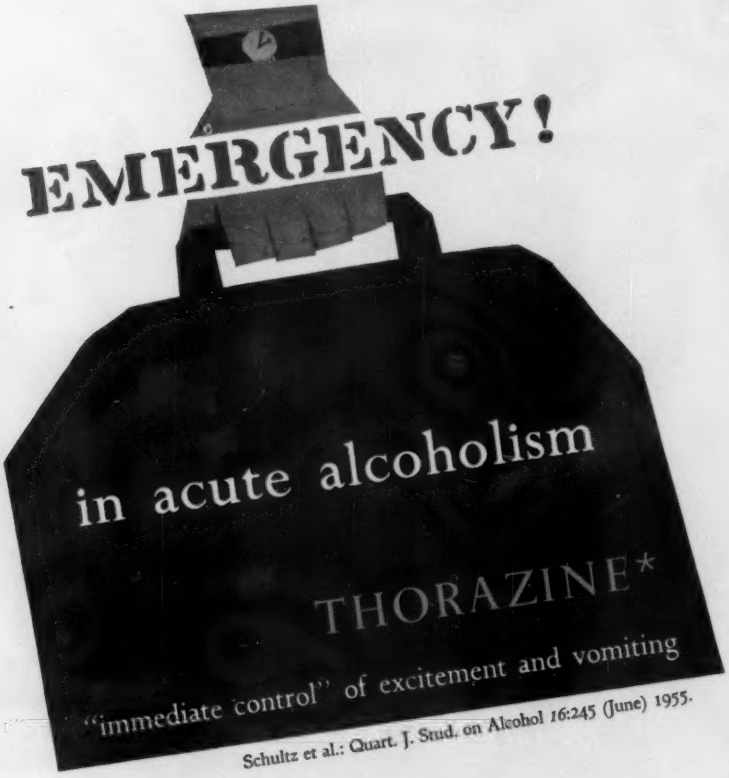
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Schultz et al.: Quart. J. Stud. on Alcohol 16:245 (June) 1955.

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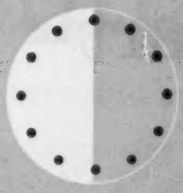

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*Breakey, R. S.; Holt, S. H., and Siegel, D.: J. Michigan M. Soc. *54*: 805, 1955.

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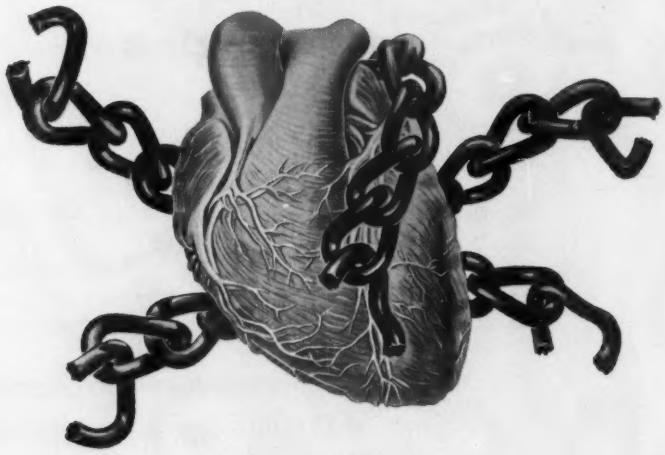
to break the chain, so heavy on his heart--



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let him actively enjoy life . . .

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Attacks gradually become less frequent and less severe with Nitralox maintenance therapy. The patient gains new confidence and is no longer overconscious of his heart. His range of activity is widened to include most of his normal occupational and recreational endeavors.

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References: 1. N.N.R. 1954, p. 107. 2. J.A.M.A. 153:1516 (Dec. 26) 1953.

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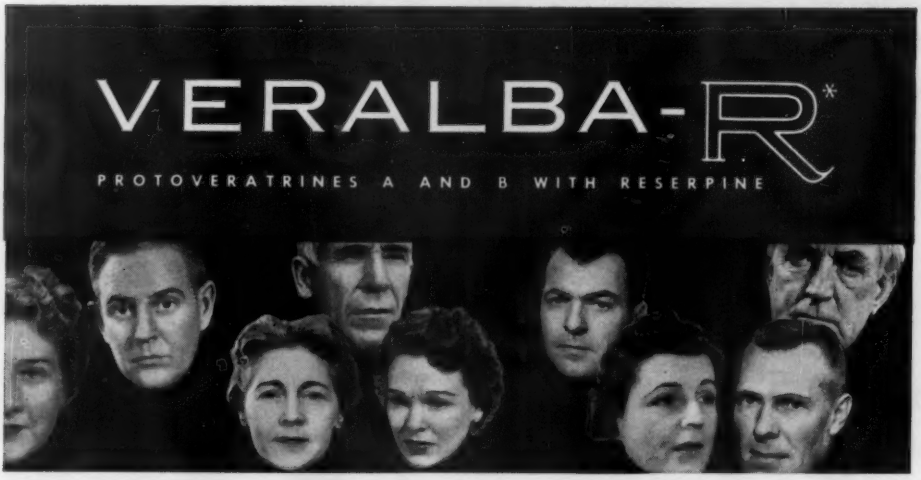

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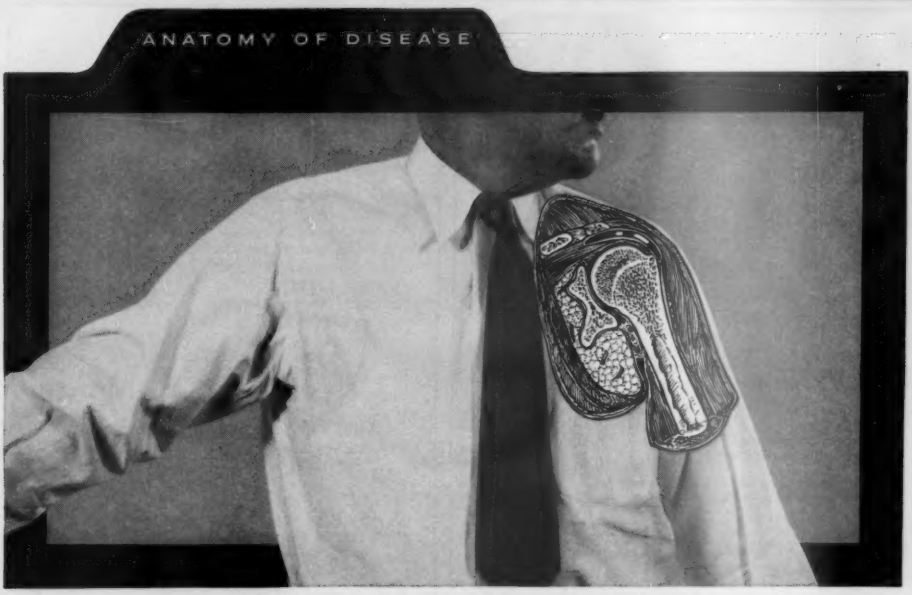

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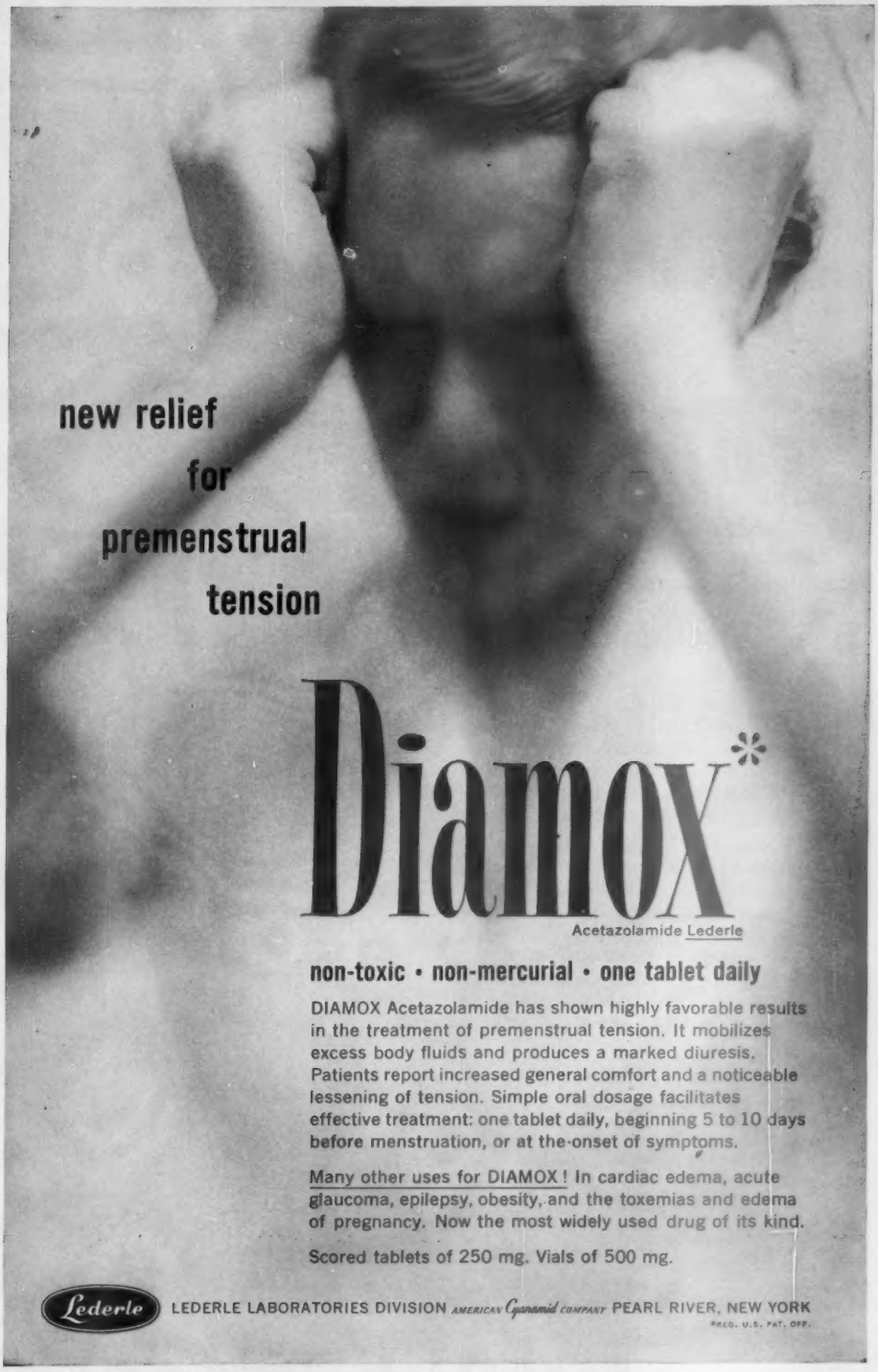
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